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THE PATHOPHYSIOLOGY AND TREATMENT OF SUBARACHNOID HEMORRHAGE IN THE CYNOMOLGUS MONKEY

BY

© WILLIAM LEGGET RITCHIE

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled THE PATHOPHYSIOLOGY AND TREATMENT OF SUBARACHNOID HEMORRHAGE IN THE CYNOMOLGUS MONKEY submitted by WILLIAM L. RITCHIE in partial fulfilment of the requirements for the degree of Master of Science in Experimental Radiology.

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Supervisor

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Date ....June 18..... 1979

ABSTRACT

The effect of a treatment regime comprising hypertension induced with dopamine, volume expansion using autologous blood and human serum albumin, and ventilatory support on the pathophysiology of subarachnoid hemorrhage (SAH) in a cynomolgus monkey model has been studied. Two experimental groups, a pilot group and main treatment group with a total of 22 monkeys are reported. The animals from the main treatment group with SAH are compared with a comparable group of 5 animals previously studied in this laboratory. Cerebral blood flow (CBF), vessel calibre, intracranial pressure (ICP) and other pertinent physiologic parameters has been measured during all experiments.

Results reveal a significant improvement in morbidity and mortality of the animals treated post-SAH compared to the untreated group. The improved survival is associated with return of CBF and vessel calibre towards pre-SAH levels. The contribution of each treatment parameter to the overall efficacy of the treatment regime is not demonstrated in the study. Linear regression analysis of vessel calibre in relation to CBF reveals a poor fit, despite adjusting for changes in blood pressure, central venous pressure, and ICP. This supports the hypothesis that microvascular changes have a major role in the control of CBF post-SAH when moderate vasospasm (30 - 35%) is present.

Despite the increased CBF in the treatment group

compared to the "control" group, an increase in cerebral perfusion pressure with treatment compared to the "control" group is not seen. This suggest that the benefit of the treatment regime may be the result of positive inotropic effects on the heart or a local effect on the cerebral vasculature. The significant contribution of ventilation to the overall survival is acknowledged.

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CHAPTER ONE : INTRODUCTION

The annual incidence of subarachnoid hemorrhage (SAH) has been reported as ranging from 7 to 16.8 cases per 100,000 population(1,2), and the most common cause is a ruptured saccular aneurysm at the base of the brain. With the advent of microsurgical techniques, intracerebral aneurysms can be treated. However a large number of patients die pre-and post-operatively or are left crippled by ischemic infarction of vital central nervous system structures. Although the precise etiology of the ischemia is unknown, many workers attribute it to angiographically demonstrable vasospasm. Much research in the past decade has been directed at improving cerebral blood flow (CBF) post - SAH in hope of averting the impending infarcts. The majority of such treatments have involved pharmacologic, mechanical, operative and ventilatory mechanisms, and have been directed at controlling vasospasm following SAH.

This present work concerns a study of one of the current treatment regimes to assess its effect on the pathophysiology of SAH. Previous work in this laboratory (3,4,5) has centered around the pathophysiology of SAH in a cynomolgus monkey model monitoring: CBF; vessel calibre; intracranial pressure (ICP); blood pressure; ventilation; morbidity to various volumes of SAH; alterations in $PaCO_2$, and alterations in blood pressure. By using this established model of SAH and by employing the findings of Rothberg et al

(6) as a control, the effect of a treatment regime consisting of hypertension, volume expansion and ventilatory assistance will be evaluated relative to its effect upon the pathophysiological sequelae of a given volume of SAH.

Virtually all treatment regimes to prevent ischemic infarction in the aftermath of SAH are based on theories to ameliorate vasospasm. Thus it is important to review the current knowledge of cerebral vascular anatomy and physiology, and also to review the current status of vasospasm.

I ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Two general types of arteries comprise the cerebral arterial circulation; superficial or conducting arteries, and the nutrient or penetrating arteries (7). Saunders and Bell (8), by means of x-ray microscopy, demonstrated that the penetrating vessels can be further subdivided into a palisade which supply the cortical capillary bed, and longer transcerebral vessels which enter the white matter and terminate in a periventricular plexus. These authors suggest that although these vessels are commonly called cortical arteries, they should be viewed as regulatory arterioles as the diameter of most ranges from 30 to 70 microns. Sundt (9) states that the presence of individual arterioles of this diameter supplying the nutrient capillary beds supports a functional role, and that they may be the primary site of autoregulation.

The superficial or conducting arteries include the carotid, middle cerebral, anterior cerebral, vertebral, basilar, and posterior cerebral arteries, and their vast networks of anastomosing branches on the brain's surface.

Fluorescent and electron microscopy has supplied a great amount of morphologic evidence of a rich nerve supply to these large conducting vessels (10,11,12,13). An anatomic association of the noradrenergic nerve fibres with small intraparenchymal blood vessels has been established using dopamine beta-hydroxylase immunofluorescence and catecholamine histofluorescence (14,15). Physiologic studies with regard to the precise effect of the sympathetic nervous system on CBF is less convincing. Although many authors support a role of the sympathetic nervous system in the control of cerebrovascular tone, autoregulation, and metabolic control of CBF (16,17,18,19) other studies do not support this role (20,21). A recent study by Heistad et al in monkeys, cats, and dogs (22) demonstrates an inability to confirm any effect of the sympathetic nervous system on cerebral vascular tone, and also an important species variation in response to sympathetic stimulation which could account for the controversial findings in various studies and which questions the validity of extrapolating animal results to the human model in this topic.

In 1963, Wolff (22) in a review of the current knowledge of the cerebral circulation, called the highly reactive pia-arterial vessels the "floodgates" of the cerebral circulation indicating his assumption that they had a major role in the control of cerebral blood flow. More recently, Mchedlishvilli et al (24) stressed the contribution of each different part of the cerebral vascular

system to CBF.

In 1971, Shapiro et al (25) performed dynamic pressure measurements in the cerebral circulation in cats and documented that 39% of the fall in pressure is in the vessels up to the large surface vessels (equal to or greater than 450 microns in diameter). Then there is a relatively small pressure head loss of 10% between these vessels and the penetrating arterioles (40 to 50 microns in diameter). The last 40% to 50% is lost in the microvasculature below the surface. Stromberg and Fox (26) confirmed this finding and further noted that as blood pressure is increased, a greater pressure head loss is shifted to the microcirculation downstream from the surface arterial vasculature. However, Sundt (9) feels that these studies on the cat are invalid when extrapolated to humans because of the presence of the rete mirabile in the cat, and that a drop of 10% to 18% between the common carotid and the parietal branches found by Bakey and Sweet (27) in humans is more valid. Thus, the majority of the resistance is distal to the superficial pia-arachnoid vessels in the physiologic man and is most likely in the penetrating arterioles. The work of Shapiro et al does, nevertheless, support the concept that the arterial network in the pia-arachnoid functions as a pressure equalization reservoir and acts by maintaining an adequate perfusion pressure for the penetrating arterioles. The anatomic studies already referred to demonstrate that it is these conducting vessels

in the pia-arachnoid which receive the majority of the adrenergic nerve supply.

These physiologic and anatomic studies do not bring one any closer to resolving the contribution of spasm in the conducting vessels to the ishcemic changes after SAH. They do, however, give an idea of the limitations of assessing only angigraphically demonstrable vasospasm, and of directing treatment solely at vasospasm. Thus, with the development of accurate CBF measurement techniques (28), a much more sensitive and direct method of assessing the condition of the cerebral circulation has been developed. Further, the use of CBF measurements can be used to accurately assess the pathophysiologic responses to SAH and to establish optimal treatment modalities in the patient or in the experimental model of SAH.

II NATURE AND ETIOLOGY OF VASOSPASM

The nature and specific cause of vasospasm is still the source of many contradictions in the literature. Many authors (29,30,31,32) support a biphasic nature of vasospasm which in experimental models occur within 5 to 10 minutes, relaxes in 30 minutes to 2 hours, then reoccurs 3 to 24 hours later, lasting up to one week or more. Other reports (33,34) would support a prolonged intense vasospasm which is even more intense after several days. Conflicts as to the severity and nature of vasospasm seen is often dependant on the amount of mechanical stimulation of the vessels in the

separate experimental models. Several clinical papers (35,36,37) do not support this application of the biphasic nature of spasm to man, and indicate that it is not seen in the first 24 hours, is maximal around 1 week, and is usually gone by 12 days post-SAH. A shortcoming in most of these studies is a lack of correlation of the spasm with CBF measurements.

Multiple blood factors (norepinephrine, histamine, prostaglandins, serotonin, hemoglobin), are capable of causing vasoconstriction of cerebral blood vessels in man. The hypothesis that a spasmogenic substance might be produced by the blood components in the subarachnoid space by sequential chemical changes, and be related to the clinical time sequence of vasospasm has been considered in the design of many experimental studies (38). The genesis of early vasospasm is suspected to be the result of mechanical factors (39,40,41) and chemical factors (42,43,44) in the blood. Serotonin has received the greatest attention in the literature (45,46,47,48,49) as the agent involved in acute and late vasospasm. However, in-vivo studies in this laboratory using physiologic doses of serotonin could not corroborate its precise in-vitro vasoconstrictive nature (50). Other work (51,52) has supported the view that serotonin is involved in early transient vasospasm but not in the more prolonged late vasospasm. Recent reports (53,54,55) suggest that hemoglobin could be the major chemical factor involved in spasm seen post-SAH.

The place of the sympathetic nervous system in the etiology of vasospasm due to SAH is uncertain, and its anatomic presence is seen by some as simply a buffering system for circulating catecholamines in that the granulated vesicles absorb the circulating catecholamines.

III CORRELATION OF VASOSPASM WITH CBF, MORBIDITY AND MORTALITY

The cause and effect relationship between vasospasm and decreased regional cerebral blood flow (rCBF) and its correlation with morbidity and mortality from SAH has been investigated by many workers in this field.

The incidence of radiographic vasospasm following aneurysmal rupture ranges from 30 to 50% (56,57). The incidence is slightly greater, (40 to 65%) after the operative treatment of ruptured cerebral aneurysms (57,58).

In a large co-operative study (59) no correlation was found between the occurrence or severity of vasospasm and the age of the patient, the presence of hypertension, generalized arterioschlerosis, diabetes, or the size of the aneurysm. However, it has been found that the incidence of vasospasm is greater in aneurysms of the internal carotid artery, and least common with aneurysms of the middle cerebral artery.

In 1975, Millikan (60) reviewed the literature on vasospasm and highlighted the many false assumptions made

and the minimal clinical and pathologic correlation cited. In his own review of 198 cases he demonstrates a lack of correlation between vasospasm and a specific clinical picture or mortality. However, it is possible that a correlation could have been found if the degree of vasospasm, rather than the presence or absence of vasospasm had been considered.

Many studies which assess the correlation of neurological status and mortality with vasospasm, have also utilized CBF measurements in the study of patients with ruptured cerebral aneurysms. A unanimous finding is that CBF is decreased post-SAH. Zingesser et al (61), in a study of 19 patients demonstrated a poor correlation between rCBF and the presence of absence of spasm, although in some cases the correlation was striking. Bergvall et al (62), in a study of 57 patients and Weir et al (63), in a study of 32 patients, both employing 133Xenon clearance technique for CBF measurement found no correlation between vasospasm and rCBF.

Schneck (64) has suggested that the vasospasm seen post-SAH is not the most significant cause of cerebral infarction and that the addition of therapeutic and diagnostic procedures, intracranial hypertension and systemic hypotension combine with vasospasm to produce cerebral infarction.

Other reports (65,66) support a correlation between rCBF or morbidity with vasospasm when the more severe groups

are separated from those with mild to moderate vasospasm. Further Grubb et al (67) as well as showing a correlation between severe vasospasm, decreased cerebral blood flow and ischemic deficits, demonstrated that the cerebral vascular volume is increased in the presence of vasospasm and decreased rCBF, which suggest that the smaller vascular structures have dilated and that the superficial extraparenchymal vessels are controlling the CBF. In a retrospective co-operative study (59) of 274 patients with SAH, a correlation between neurologic condition and the presence of spasm was noted. Vasospasm was present in 22% of grade 1 patients, 33% of grade 2 patients, 52% of grade 3 patients, 53% of grade 4 patients, and 74% of grade 5 patients. In this study, severe deficits were occasionally present with no evidence of vasospasm. Since this time the correlation of CBF with clinical grade or ischemic deficit in the more severe cases of vasospasm has been reported widely (68,69). These findings support the view held by investigators in this area that if spasm is severe, then CBF is decreased and neurological grade is generally poor, but in cases with less marked spasm, a correlation is more difficult to make.

Similarly, in early reports (59), a relationship between mortality and vasospasm could not be established. However, in a more recent study, (65) when patients dying soon after reaching hospital were excluded from the analysis, a highly significant correlation could be

demonstrated.

IV TREATMENT OF SAH

The treatment of SAH, which includes a direct attack on the aneurysm with microsurgical techniques and methods for lowering the ICP, has concentrated mainly on increasing CBF by methods which reduce cerebral vasospasm. If cerebral vasospasm and the resulting cerebral infarction could be controlled in the period after SAH, then operative intervention could be carried out immediately post-SAH thereby minimizing the chance of a rebleed. At this time, many neurosurgeons are reluctant to operate in the face of marked vasospasm and/or a poor clinical grade because of the poor post-operative prognosis due to the increased risk of cerebral infarction.

A. General Treatment Modalities

A good review of all agents and methods used in the treatment of intracranial arterial spasm up to 1973 has been made by R.H. Wilkins (70).

Current studies (71,72) indicate that cyclic nucleotides, 3'5' adenosine monophosphate (cAMP) and cyclic 3',5' guanosine monophosphate (cGMP) are important in the role of contraction and relaxation of vascular smooth muscle (Fig. 1). Increasing the cAMP results in binding of ionic calcium in the myoplasm, which decreases the myoplasic ionic calcium causing relaxation of the actin and myosin filaments of the vascular smooth muscle. cAMP is decreased by

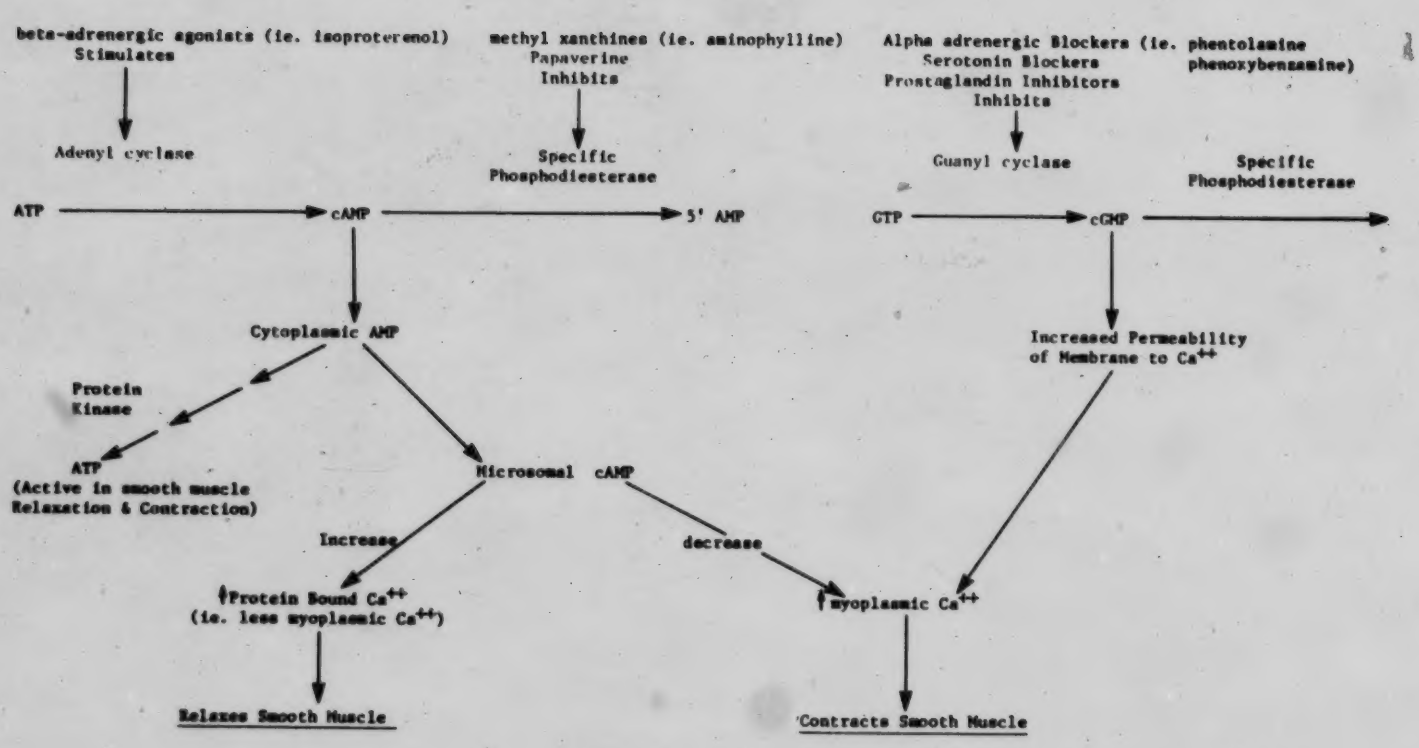

FIG. 1. Schematic Representation of the Cyclic Nucleotides and Smooth Muscle Function

activating the specific phosphodiesterase system which hydrolyzes it to 5' AMP. Thereby, agents which activate or increase the concentration of cAMP would result in vascular smooth muscle relaxation. Conversely, increasing the cGMP increases the permeability of the cell to ionic calcium in the extracelluar fluid. Movement of the ionic calcium into the myoplasm initiates contraction of the actin and myosin filaments. Inhibition of the enzyme guanyl cyclase which converts guanosine triphosphate to cGMP would result in less cGMP and therefore smooth muscle relaxation.

With this biochemical base investigators have used beta-adrenergic agonists (i.e. isoproterenol and salbutamol), which activate the enzyme adenyl cyclase, thus stimulating the formation of cAMP, in an attempt to relax contracted vascular smooth muscle. These agents have been used alone (73) and in combination with agents which inhibit phosphodiesterase (i.e. aminophylline, papaverine, and chloramphenicol) theoretically resulting in an even larger pool of cAMP because of the prevention of its metabolism. Studies done in experimental animal models (74,75,76) using isoproterenol and aminophylline in combination relieved acute and chronic vasospasm. Uncontrolled clinical trials (77,78,79) generally demonstrate favourable results, however, CBF studies were often not done and the study groups were small. A large control study has yet to be published. Recently Sundt (80) has suggested that the benefit of these agents may have been through their

inotropic effect on the heart rather than the postulated effect on cAMP. These beta-agonists also have systemic side effects (particularly cardiac) which have required the simultaneous use of lidocaine HCL to prevent the development of cardiac arrhythmia. Also recently, aminophylline has been shown to be detrimental in the first 16 hours following carotid ligation in an experimental animal model (81).

Alpha-blocking agents (i.e. phenoxybenzamine, and phentolamine) inhibit guanyl cyclase and have been used in experimental models. Nagai et al (51) employed an alpha-blocker in combination with an anti-serotonin agent and found they relieved early vasospasm but not late vasospasm. They also found that sympathectomy resulted in less marked early spasm. In other studies (82,83) phentolamine has been shown to decrease CBF and the use of phenoxybenzamine and propranolal (beta blocker) could not improve CBF in a SAH experimental model.

Following Allen's proposal (84) that nitroprusside could antagonize the contractile effect of serotonin on cerebral vessels, and that its systemic side effects could be selectively antagonized by agents such as phenylephrine, several studies of such treatment regimes have been conducted. A good review of this topic has been made by C. Rothberg (3). The experimental and clininal trials of this regime, although initially promising, have shown recently the failure of this regime to improve CBF post-SAH and in

fact, have demonstrated the regime to be detrimental to cerebral autoregulation.

Recently, Allen et al (85) has demonstrated the relatively selective effect of nifedipine on the basilar artery in dogs. Nifedipine is a new drug which theoretically blocks the influx of extracelluar calcium into the smooth muscle cell (myoplasm). A trial of this drug on dogs as shown it to relieve acute and delayed arterial vasospasm post-SAH (86). Further controlled animal and clinical trials of this medication are needed.

B. Treatment with Hypertension and Volume Expansion

The current literature supports a form of treatment employing controlled hypertension and volume expansion for ischemic symptoms post-SAH. The hypothetical mechanism of action of this treatment regime is based on the demonstration that autoregulation is impaired post-SAH (87,88,89,90). Autoregulation is the ability of the CNS to maintain the CBF at normal levels over a wide range of blood pressures and intracranial pressures. Boisvert et al (90), in monkeys, have demonstrated the passive dependance of CBF post-SAH on blood pressure. Therefore, by increasing the blood pressure post-SAH, one could theoretically maintain the CBF above the critical level at which cerebral infarction occurs.

The use of hypertension to treat cerebrovascular ischemic symptoms is not a recent idea by any means. Denny-

Brown (91), in 1951, recommended the use of hypertension in the treatment of ischemic cerebrovascular symptoms. In 1967, Farhat and Schneider (92) described four patients in which metaraminol has been used to induce hypertension to treat cerebral ischemia due to SAH in two patients, post-operative tumor surgery in one, and atheroschlerotic stenosis of the internal carotid in another. In all four cases, treatment resulted in marked improvement of the patients symptoms. The treatment of post-angiographic hemiplegia with vasopressors has also been reported (93). Since this time there has been numerous reports of the beneficial effects of hypertension in impending cerebral infarction (94,95).

Three reports describing the beneficial effects of hypertension in patients who are in the post-operative period after aneurysm surgery are of particular importance. In 1976, Kosnik and Hunt (96) described 7 patients who developed post-operative ischemic symptoms and were treated with colloid volume expansion and norepinephrine to increase the blood pressure; six of these patients made a dramatic recovery. In 1977, Giannotta et al (97) reported 17 cases in which controlled hypertension (using phenylephrine or dopamine), hyperventilation, and over transfusion with whole blood or colloid, were used to treat ischemic neurological deficits likely due to cerebral vasospasm post-aneurysm surgery. Prompt, complete reversal of the deficits occurred in 12 patients, and partial reversal in 3 patients. In 1978, Brown et al (98) described the reversal of aneurysmal

hemiplegia pre and post-operatively in 4 patients using dopamine, large quantities of intravascular fluids, and mannitol. The beneficial effect of intravascular volume expansion alone, in patients with neurological deficits associated with SAH has also been reported (99). Objective support of the need for volume expansion in patients on bed rest or post operative has been published over the years (100,101,102,103,104). Maroon and Nelson (105) have recently demonstrated in 15 patients that the red blood cell mass and the total blood volume are significantly decreased post-SAH which supports the use of red blood cells and colloids in the prevention and treatment of ischemic complications associated with ruptured intracranial aneurysms. By maintaining an optimal hematocrit in these patients, more oxygen may be transported to the ischemic areas with a given volume of CBF. Another theoretical advantage of colloid transfusion is to maintain the colloid osmotic pressure within the circulation, and thereby reduce cerebral edema. Volume expansion effects the pre-load on the heart which may under some circumstances increase cardiac output (106,107,108) and possibly thereby improve cerebral blood flow.

Hyperventilation of these patients with cerebral ischemia except in an effort to decrease ICP, is of questionable value because of the variable responses of cerebral blood vessels to changes in PaCO2 and pH post-SAH (89,109,110,111). However, it has been seen from previous

work in this laboratory (3,4,5) that the spontaneously breathing monkey has a poorer survival post-SAH than an animal whose ventilation is assisted throughout. The use of assisted ventilation as well as preventing any prolonged apneic spells, could maintain PaO2 above the normal range (greater than 100 mm Hg) while maintaining PaCO2 within the physiologic range. This would make more oxygen available to the tissues.

In the articles reviewed concerning the use of hypertension in the treatment of ischemic symptoms, different vasopressor agents have been employed. The use of dopamine as a vasopressor in some of these studies is unusual because its alpha agonist properties are small in comparison to agents such as norepinephrine and metaraminol, and often large doses must be used in order to increase blood pressure. However, dopamine does have actions which could be strategic in its ability to improve rCBF and relieve ischemic symptoms in these studies. The response or vascular smooth muscle to dopamine, either vasoconstriction or vasodilation is variable depending on the anatomic site of the smooth muscle, the state of tone in the smooth muscle and the concentration of dopamine (84,112,113,114). Dopamine has been shown to activate the adenyl cyclase phosphodiesterase system in man, both in the kidney (115) and in certain regions of the brain (116). However, as yet, its effect on cAMP in cerebral vascular smooth muscle has not been demonstrated. The activity of dopamine in causing

vasodilation had also been shown to act at a different receptor site than beta-adrenergic, cholinergic, and adenosine related agents in coronary (113), hepatic (112), and cerebral vessels (114). These unique receptors for dopamine on vessels may allow it to act on cerebral vessels when other agents can not. Finally, dopamine has been shown to inhibit the sympathetic nervous system, the role of which in cerebral vasospasm has not been well defined (117,118).

Although the treatment regimes employing hypertension and volume expansion have a valid theoretical basis and results which suggest it is beneficial, no controlled studies of its use in SAH have been published.

V RADIOGRAPHIC CONSIDERATIONS

In the literature, no good correlation has been reported between mild to moderate vasospasm and changes in rCBF post-SAH. This finding could result from a true lack of correlation between these parameters due to the contribution of microvascular changes to decreases in rCBF post-SAH, or possibly from the inability of the angiography and measurement system to accurately reveal small changes in vessel size. In some studies (68) though corrections for changes in x-ray magnification between films has been reported, no correction for changes in film, screen, developing, or exposure factors has been made. Further, the possible alterations in vessel calibre and CBF measurements due to contrast medium and type of injection has not been

considered. Also, the limitations of each individual system with regard to resolution and and reproducibility of the films has not been documented. If one is only concerned with gross changes (±30%) in vessel calibre, then these factors may not be vital. However, in the experimental model when small vessels are to be measured and when small changes in vessel calibre are to be considered, then these factors should be assessed. Further, to decide on the contribution of mild to moderate spasm to changes in rCBF in the post-SAH period, the accuracy of the vessel measurements is of paramount importance.

The contention that severe vasospasm results in decreased CBF, ischemic deficits, and increased mortality, is supported in the literature. Most treatments are directed at relieving this vasospasm to improve CBF so that cerebral infarction does not occur.

The purpose of the present work using a cynomolgus monkey model is to assess a treatment regime employing hypertension induced with dopamino volume expansion using autologous blood and human serum albumin, and ventilatory assistance to evaluate its effects on the pathophysiology of a specific SAH volume as demonstrated by Rothberg et al (6).

CHAPTER TWO : MATERIALS AND METHODS

This section describes the material and methods used in the two studies comprising this work. Study I is preliminary work involving 8 monkeys which served to establish the treatment procedure and protocol, and to complete the development of the operative skills required in this experimental model. Study II involves 14 monkeys and concerns the evaluation of the selected treatment regime.

Generally the techniques described were used during both studies, exceptions are indicated as appropriate.

I ANIMAL PREPARATION

Twenty-two female, cynomolgus (Macaca fascicularis) monkeys with body weights in the range of 2.5 to 3.7 Kg. were utilized.[1] Monkeys were used in the present investigation because of the close similarity of their cerebral circulation to that of man (Fig. 2). The animals were received into the vivarium at least three weeks prior to experimentation. Ten days to three weeks prior to an experiment whole blood was removed from each monkey and stored at a temperature of 2 to 6 C in sterile blood bags using 7 mls of citrate phosphate dextrose or citrate dextrose as the anticoagulant. At the time of bleeding 50-75 mls of 0.9% saline was infused to prevent a hypotensive

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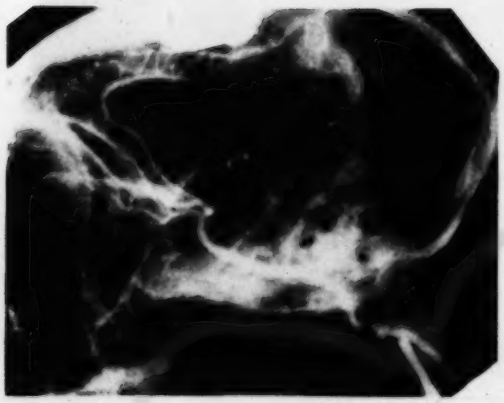
1. Obtained through Primate Import Corporation, Port Washington, New York



1. internal carotid
2. opthalmic
3. posterior communicating
4. middle cerebral
5. pericallosal

Fig 2a) Lateral angiogram and diagram of cerebral arteries seen with a carotid injection of contrast medium in the cynomolgus monkey

1. vertebral
2. basilar
3. posterior cerebral
4. posterior communicating
5. internal carotid
6. middle cerebral
7. anterior cerebral
8. pericallosal

Fig 2b) Basal view of carotid angiogram and diagram of the cerebral arteries in the cynomolgus monkey. Note: The anterior cerebral arteries join to form only one pericallosal vessel.

episode and 100 mgms. of iron[1] was given. Blood samples for hematocrit and serum electrolytes were obtained and the animal weights were recorded.

Prior to the experimental study the animals were fasted for 6 hours, phencyclidine HCL[2], 3 mgm per Kg IM, was given at the vivarium prior to transportation. At the laboratory, the animals were shaved as required and intubated with a No. 16 Rusch or No. 5 Portex endotrachael tube and allowed to breath spontaneously a mixture of 2 to 1 nitrous oxide to oxygen at a flow rate of 3 litres per minute.

In the post-SAH period, ventilation was assisted using a Harvard ventilator[3] with gallamine 1 mgm per Kg IV[4] as the neuromuscular blocking agent. In the preliminary study d-tubocurarine[5], 0.9 mgm per Kg I V was used as the neuromuscular blocker. Respiratory tidal volume and rate were monitored by means of a pneumotachograph[6] attached directly to the endotracheal tube, the output was monitored using a Beckman Dynagraph, type R, Recorder.

Body temperature was maintained between 36 - 38° by means of a heating pad underneath the monkey, and recorded using an esophageal thermometer[7]. Lead II of a standard limb

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1. IMFERON, Fisons Pharmaceuticals
2. SERNYLAN, Bio-Ceutic Laboratories
3. Model No. 613 Harvard Apparatus Co. Ltd,
4. FLAXEDIL, Poulenc Ltd.
5. TUBARINE, Bourroughs Wellcome Ltd.
6. HEWLETT PACKARD, Vertex Series 400 UR, HP 47303A
7. TELE-THERMOMETER, Yellow Springs Instrument Company

lead electrocardiogram was utilized, and monitored separately on a ECG recorder[1].

II SURGICAL PREPARATION

Femoral artery catherization was carried out by means of a cutdown, and a No. 4 polyethylene catheter was introduced. Shortly after the placement of the tip of this catheter in the mid-abdominal aorta, 0.8 mls. blood was obtained in a heparinized syringe for gas analysis[2] (PaO_2, $PaCO_2$, pH). Adjustments in the dead space of the animal were made as necessary in order to keep the $PaCO_2$ between 36 - 44 mmHg. The arterial catheter was coupled to a Statham 23 dB pressure transducer for continuous monitoring of the blood pressure. Intermittent flushing of the catheter with 0.2 ml of 0.9% saline with heparin (5 units/ml) was carried out in order to prevent clotting. This catheter was also used to take blood samples for hematocrit and blood gas analysis prior to each CBF determination and also to take blood for SAH induction.

A No. 5 and No. 4 radiopaque polyethylene catheter were placed in the right and left femoral vein respectively. The No. 5 catheter was used for assessment of the central venous pressure at the level of the inferior or superior vena cava. The position of the tip of this catheter was checked by means of a chest x-ray. The No. 4 catheter was placed with

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1. SANBORN COMPANY Model 51
2. INSTRUMENT LABORATORIES INC., PH gas analyzer, Model 113

its tip in the abdominal portion of the vena cava and was used for the administration of dopamine[1]. Both catheters were coupled to Statham 23 dB pressure transducers for continous monitoring and recording.

A burr hole in the right mid-parietal region and two offset holes were made in the bone with an air drill[2] for placement of an intracranial pressure recording device developed by Rothberg and co-workers (3) in this laboratory (Fig. 3). Bleeding from the diploic veins was arrested by means of bone wax. Two modifications in this device were made. The 3-way stop-cock connected to the device was removed to prevent escape of saline or entrance of air into the system at this point. Also silicone cement was applied about the periphery of the membrane in addition to the "o" ring situated there, to assure a good seal between it and the metallic body of the ICP device. A small amount of sterile lubricant was placed on the dura to assure planar contract between the dura and the membrane of the device. Pressure was measured using a Statham 23 dB transducer and recorded on the Beckman Dynograph. A screw on top of the device assured solid fixation of the device to the calvarium and a tight seal was assured by means of an "o" ring and silicone cement. The scalp was then resutured about the device.

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1. INTROPIN, Des Bergers Ltd.
2. Hall Air Surgery R Instruments, Microdrill

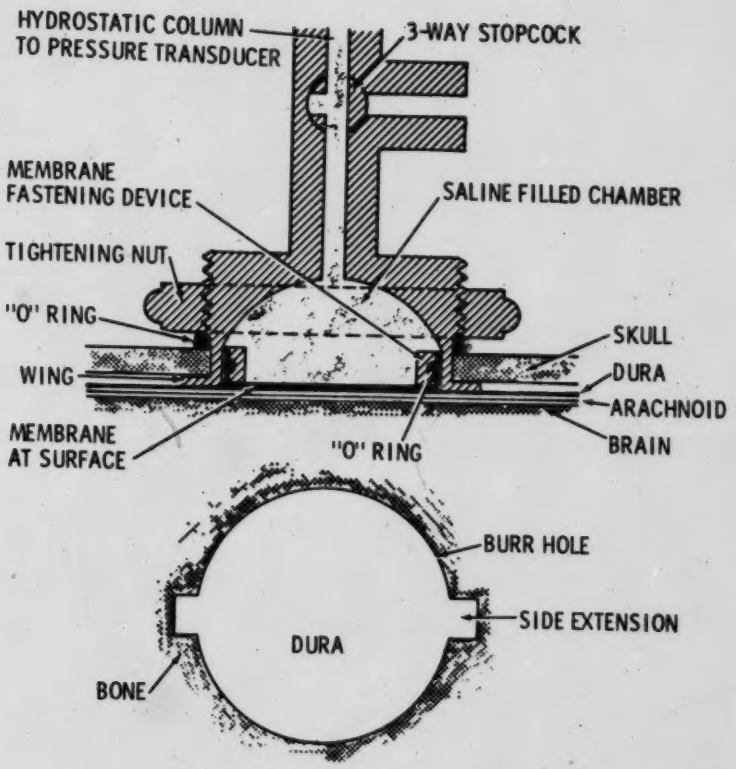

FIG. 3 Intracranial pressure device developed by C. Rothberg et al (see text for modifications).

A twist drill hole was made in the frontal bone using a 1.5 mm diameter bit, approximately 1 cm cephalad to the nasion of the midline. The hole was then occluded with bone wax to stop bleeding until placement of a needle for induction of the SAH.

The left cervical dissection was then begun using a surgical microscope[1]. The dissection was made centering over the bifurcation of the common carotid and care was taken to spare any vagal nerve fibres in this region. The external carotid was clipped at its origin with an aneurysm clip. A purse string suture, using 7-0 silk with a micropoint, with an approximate diameter of 1 mm was placed in the adventitia of the common carotid 2 centimeters proximal from the bifurcation. A No. 22 gauge teflon catheter[2] was introduced through the purse string which was then fully tightened to stop bleeding without occlusion of the vessel. This catheter was connected to an automatic injector device by means of a PE 160 catheter and a three way stop-cock. Intermittent flushing of the catheter was carried out using heparinized saline (10 units/ml).

The Beckman dynagraph used to record all pressures and to record the respiratory rate and volume was calibrated immediately prior to and after each experiment. Intermittent checks of the zero points were made throughout the

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1. Codman, Mark II
2. Quik-Cath R

experiment to determine the magnitude, if any, of instrumental drift.

III Method of Simulating the SAH

The method of Weir et al (119) was employed. A circumferentially bevelled No. 19 gauge needle was introduced through the frontal twist drill hole and advanced 3 - 4 mm beyond the anterior clinoid processes and at this point lay within the chiasmatic cistern. In approximetaly 50% of cases ready flow of cerebral spinal fluid could be obtained through the needle. The position of the needle was checked by the means of fluoroscopy and on lateral and basal films. The needle was fixed at this point by means of a screw device. The hemorrhage was induced using autologous blood taken from the arterial catheter in a volume of 1.67 ml/kg body weight. The hemorrhage was given as fast as possible while maintaining the incracranial pressure below mean arterial blood pressure.

IV ANGIOGRAPHY

A. Technique

Five to seven angiographic sessions were conducted during each experiment with hand injection of the contrast medium used for the first 18 monkeys studied. At each angiographic session two lateral films in good arterial phase were obtained. Statistical analysis of measurements for 67 vessel pairs were made to determine if differences existed between the first and second film obtained. Each

angiogram utilized 1.5 ml of diatrizoate meglumine[1] 60% contrast medium.

In order to standardize the films further, a Cordis injector was utilized in four monkeys, (Fig. 4) and each film obtained with constant injection pressure (range 10 to 15 p.s.i.), constant exposure time (immediately following completion of the injection), and a constant volume of contrast medium (range 1.5 to 3.0 mls). Measurements for forty vessel pairs from this sub-group were also analyzed to determine if differences existed between the first and second films obtained at each angiographic session.

The x-ray equipment utilized was Philips[2] with a 0.6 mm nominal focal spot. Two millimeters of added aluminum filtration was used. The films were exposed at 6 MAS and 45 KVP with Kodak RP film and Dupont Par Screens. The film was processed through a Kodak M4 RP converted with Kodak chemistry. The tube-film distance used was 152 cms, and the object-film distance 2 to 3 cms. In order to ensure that film quality, exposure, and developing were kept constant, a radiopaque brass plate with 1 mm holes and covered with aluminum was designed (Fig. 5). Comparison of the hole diameter between the "control" and later angiograms allowed for correction for any changes in these factors. Changes in magnification were controlled between films by fixation of

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1. Reno-M-60
2. Rot 250/40

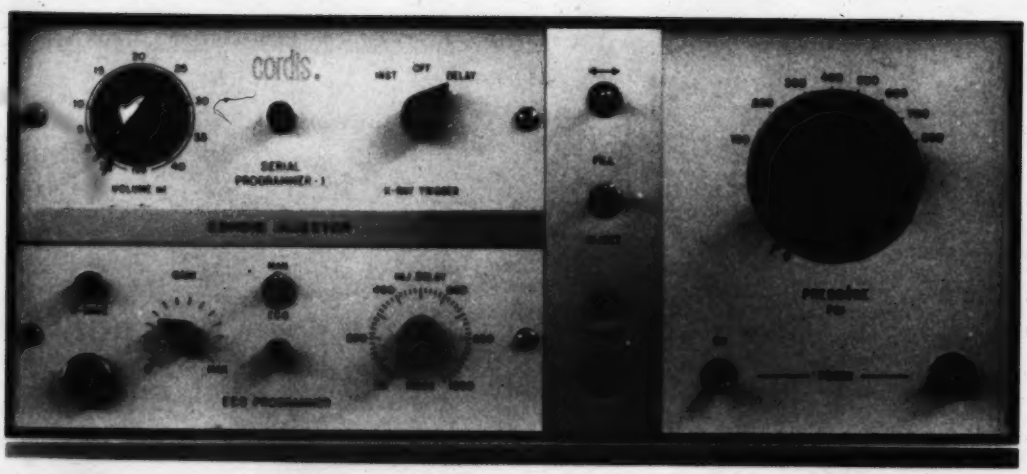

FIG. 4 Cordis[R] contrast medium injector used to give a set volume of contrast at a set pressure.

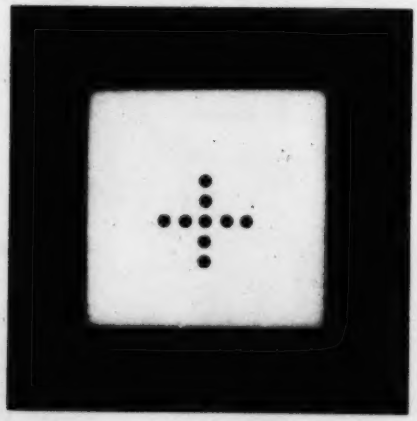

FIG 5a) Radiograph of control plate

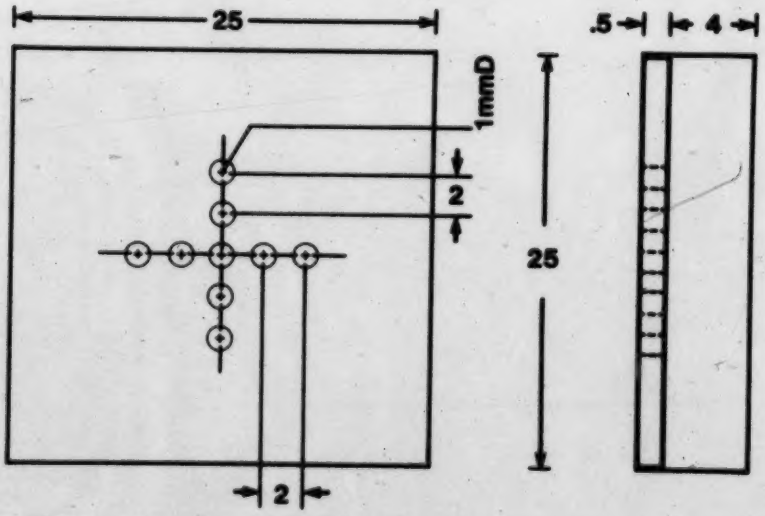

FIG. 5b) Schematic diagram of 0.5mm brass control plate with 4mm of aluminum fixed to it. Each hole measures 1 mm and the plate measured 25 by 25mm.

monkey's head in relation to the film and tube throughout the experiment.

B. Measurement of Vessel Calibre

All measurements on the films were made using a 10 power micrometer lens system[1]. A mean diameter for the holes in the "control" plate was established from twenty measurements obtained by measuring from left to right, then right to left across the 5 horizontal holes, then from top to bottom and bottom to top for the 5 verticle holes (Fig. 5). Comparison of the mean diameter of the holes on this plate between films facilitates correction for changes in film quality, exposure and developing.

Intraluminal diameters of the large capacitance vessels were measured, viz: the internal carotid immediately below the opthalmic artery (ICBO), the internal carotid immediately above the posterior communicating (ICAP), the proximal middle cerebral (MCA), and the proximal pericallosal (PPC) (Fig. 6). Each vessel was measured six times, each measurement requiring visual definition of the edges of the vessel, and these values were used to calculate a mean vessel diameter. All measurements were made "blindly" with the observer not knowing which film in a series was being measured. For a single observer the average coefficient of variation (percent standard deviation) of

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1. NIKON, Nipon, Japan

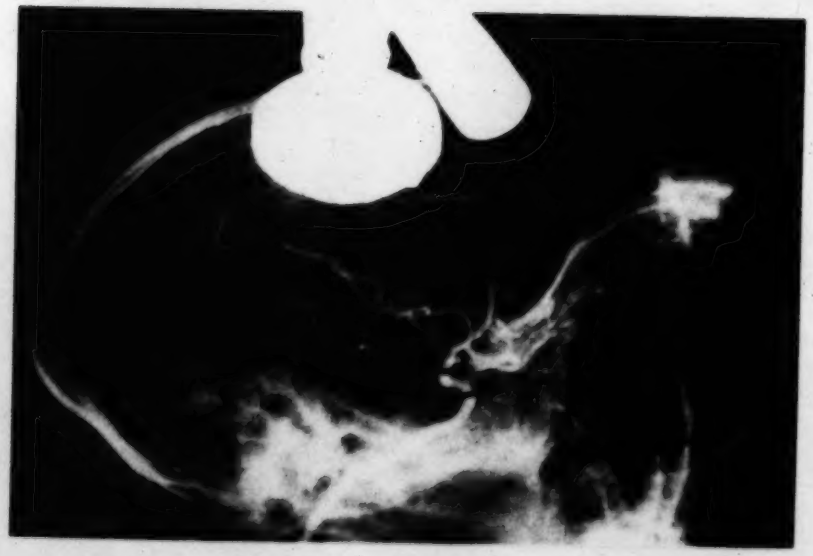

FIG. 6. Lateral Angiogram with the four sites for vessel calibre measurements marked.

this measurement system was calculated from the data on the first 96 vessels measured. Subsequent to this standardization procedure, any set of measurements with a coefficient of variation greater than two standard deviations from the established population mean was remeasured.

C. Errors in Vessel Measurement

As already described, a radiopaque brass plate was placed on each cassette to correct for changes in film, screen, exposure and developing factors.

Also, a calculation was done of the possible variation in magnification of the vessels due to changes in position of the monkey's head in relation to the tube and the cassette. It was estimated that the maximum (although unlikely) possible lateral movement of the monkey's head was 2 cm. in either direction. Hence, with a tube film distance of 152 cm. and an average object film distance of 3 cm., the magnification would be:-

$$\frac{TFD}{TOD} = \frac{152}{149} = 1.02$$

If there was 2 cm of movement in either direction the respective magnifications of the object would be:-

$$\frac{152}{147} = 1.03, \text{ or } \frac{152}{151} = 1.01$$

Thus a possible difference between magnification of the 1 mm vessel would be 0.02 mm, a value well below the resolution

of the film screen system used. Although an exact measurement of the resolution in line pairs per mm for the film screen combination used was not made, it would be at most, 10 line pairs per millimeter. Hence the zone of unsharpness about any given border of contrast would be around the value of 0.1 mm and the edge of any image measured would be taken as the midway point of the zone of unsharpness of 0.05 mm (120), which is much greater than the possible changes due to magnification as a result of inadvertent lateral movement of the monkey's head.

The total resolving power of the system is dependant on the factors contributing to the unsharpness of the image. The factors contributing to this are geometric unsharpness (penumbra and motion unsharpness), absorption unsharpness, and unsharpness due to image conversion (screen, film, and radiographic mottle). The major contribution is from screen film combination. The best way measure this is by the modulation transfer function, but this parameter has not been measured in this study.

As well as unsharpness of the system, changes due to variation in magnification, developing, exposure, and film-screen characteristics contributing to the inaccuracy of measuring the vessels, the observer characteristic response in interpretating the edge of the image each time also has a very significant contribution to the limitations of the measurements.

V CEREBRAL BLOOD FLOW STUDIES

The methods of handling, dispensing, administration, and detection of 133 Xenon (133 Xe), and subsequent calculation of cerebral blood flow has changed little over the past 6 years in this laboratory. Since these methods have been described in detail elsewhere (5), only a brief review will be given here.

A. Handling and Dispensing of 133 Xe

Intra-arterial injection of 133 Xe using the technique of Lassen and Ingvar (28) for the measurement of CBF has been used in this laboratory since 1972. 133 Xe is a freely diffusible radioactive gas with a physical half life of 5.3 days[1]. Since intra-arterial injection of 133 Xe is required, it is necessary to dissolve the gas in distilled water using a special apparatus developed in this laboratory (121).

B. Administration and Detection

An automatic injector device developed in this laboratory was used to inject the 133 Xe into the carotid artery (Fig. 7). This device is capable of injecting varying amounts of 133 Xe (0.2 to 0.9 mls) over a short period of time. The amount injected was approximately 2.5 to 3.5 mCi per flow measurement, and the volume of solution was varied from experiment to experiment to give this amount of

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1. Obtained from Oak Ridge National Laboratories, Oak Ridge, Tennessee.

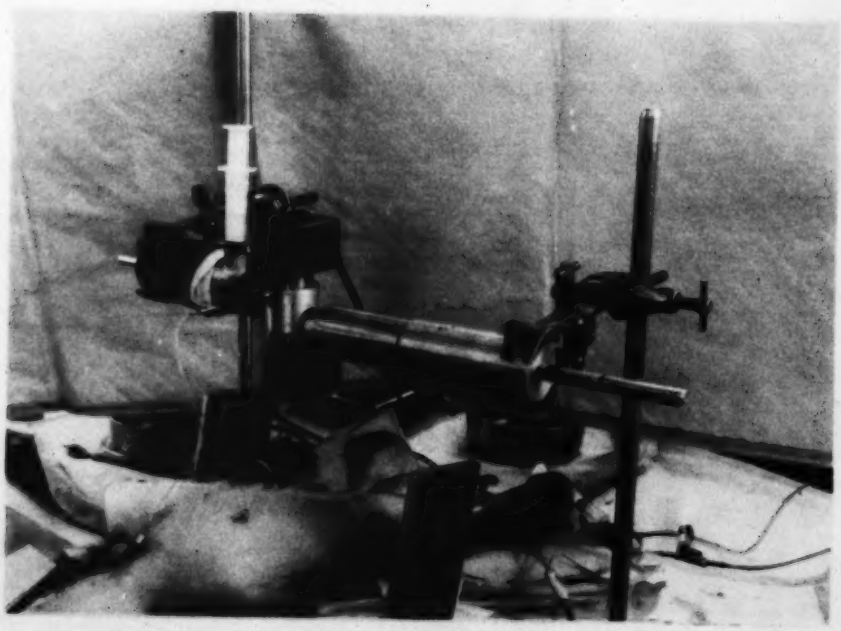

FIG. 7. Automatic Device used to Inject ^{133}Xenon Followed by a Saline Flush.

radioactivity. The injection of the 133 Xe was followed by a small saline flush (0.2 to 0.5 mls) to ensure that all the radiotracer was flushed from the catheter into the cerebral circulation.

In total seven detectors were used to record 133 Xe clearance rates from the brain. Six of these detectors were mounted as an integral unit and viewed the ipsilateral side of the head as the 133 Xe was injected. The data from the four detectors which viewed the frontal, parietal, parietal-occipital, and temporal regions were used in the calculation of mean cerebral blood flow (Fig. 8). The remaining two detectors viewed the orbit and cerebellar regions. Each detector in this assembly consisted of a 0.6 cm. diameter, 1.25 thick NaI (TI) crystal optically coupled through a plexiglass light guide to a 1.25 cm. diameter photomultiplier[1]. The detectors, spaced 1 cm. from each other, were mounted in a stainless steel collimator block with the face of each crystal recessed 7.5 cm. from the block face. An additional 1.5 cm. thick lead collimator applied to the block face ensured measurement of radioactivity from discrete volumes of brain tissue. The isoresponse curve for this multiprobe detector can be seen in Fig. 10. This detector assembly could be accurately repositioned throughout the study by using a radiopaque template aligned by means of fluoroscopy and films (Fig. 9).

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1. Philips X P1101

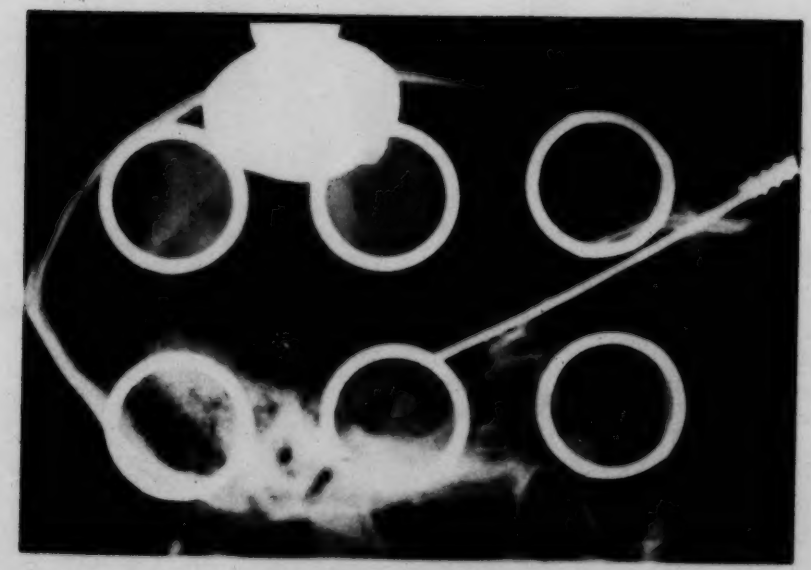

FIG. 8 Lateral Radiograph of Template which indicates the discrete areas of the brain "viewed" by the Multiprobe detector.

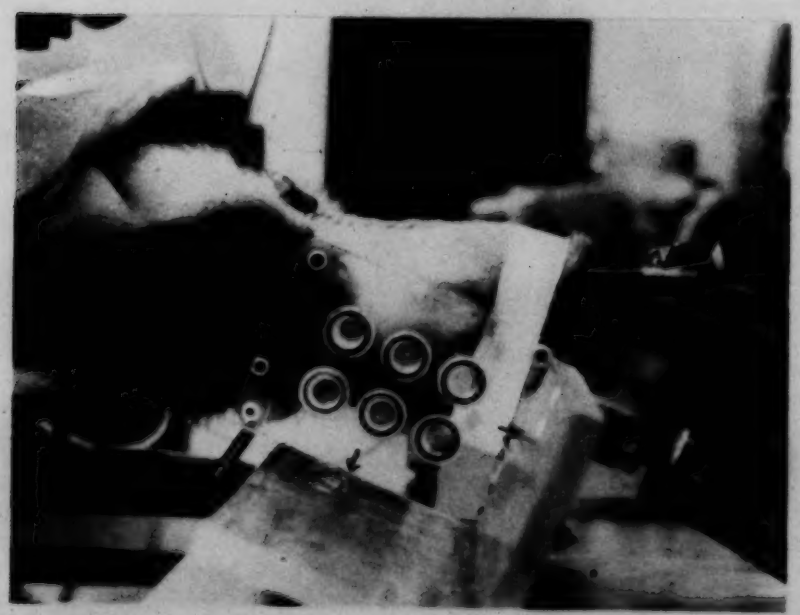

FIG.9 Template in position on Mulitprobe detector carriage immediately adjacent to monkey's head.

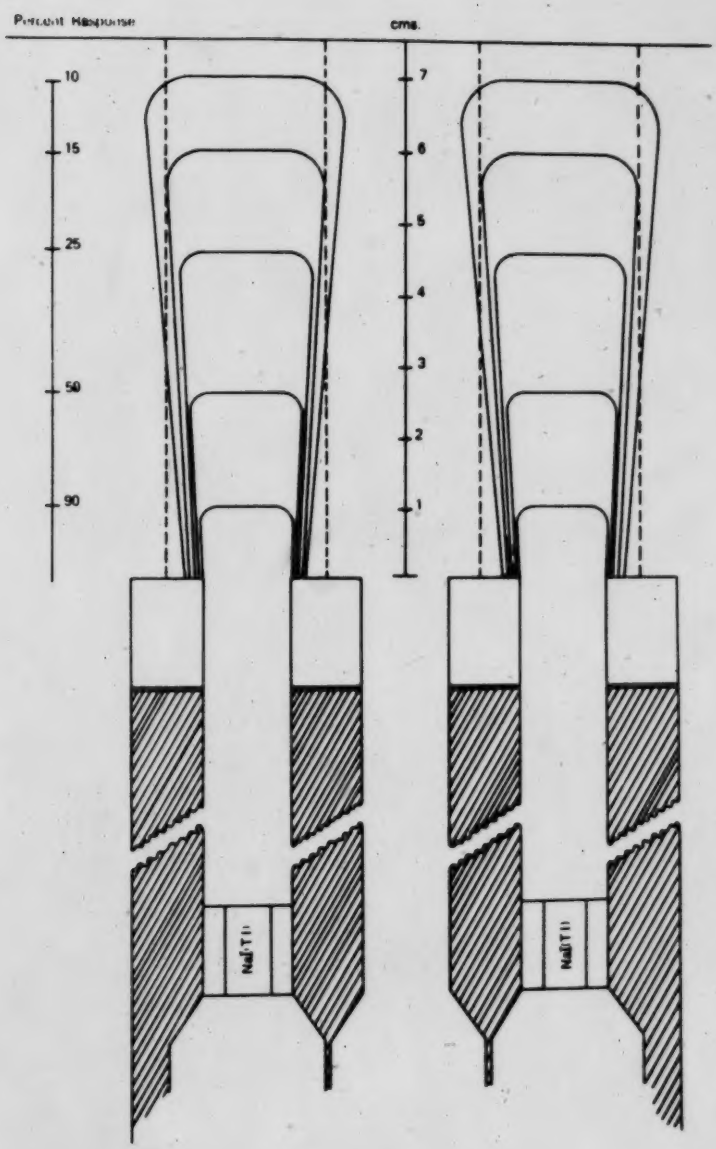

FIG. 10 Isoresponse curves for two adjacent probes in the multiprobe detector with a point source of 133 Xenon in water.

The seventh detector which viewed the contralateral hemisphere consisted of a 2.54 cm in diameter, 1.25 cm. thick NaI (TI) crystal/photomultiplier assembly, and was collimated by a lead cylinder with a 2.54 cm. diameter aperture. The isoresponse curve of this single probe can be seen in Fig. 11.

Immediately prior to each experimental study all detectors were calibrated for the 80 Kev gamma ray from 133 Xe using a multichannel analyser system. In an experimental measurement, signal outputs from each detector were routed through an amplifier and pulse height analyzer chain, and recorded at 2 second intervals using a CAMAC scaler-computer system. Each experimental measurement of 133 Xe clearance required 15 minutes; 2 minutes background and 13 minutes following the injection of the radioactive tracer. All counting rate data was accumulated on a computer disc and processed, in real-time, to display the individual clearance curves on an oscilloscope monitor in the laboratory. A schematic diagram of the electronics of the system is shown in Fig. 12.

C. Calculation of Cerebral Blood Flow

An extensive historical review and details of the basic theory underlying the calculation of CBF has been presented in previous publication from this laboratory (5).

CBF can be calculated by several different methods, viz: "height over area" or stochastic (H/A), "initial slope

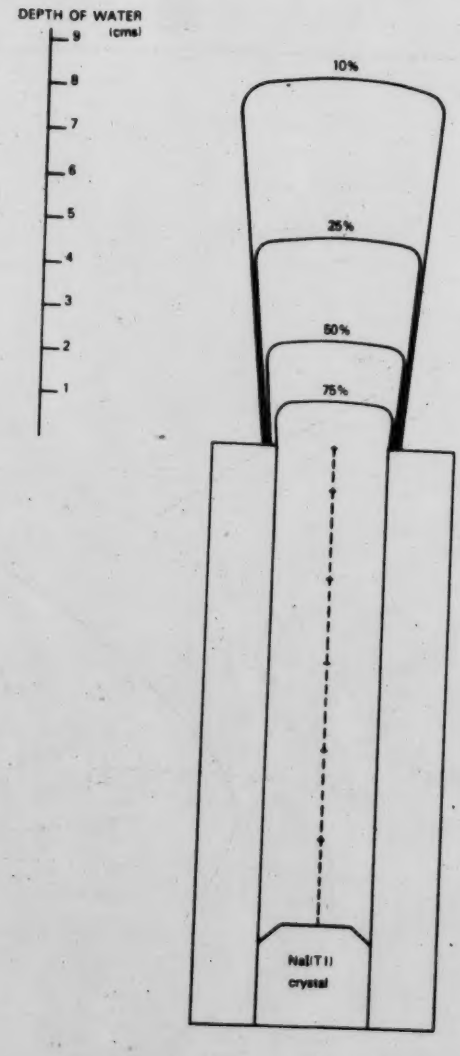

FIG. 11 Isoresponse curves for the single probe detector with a point source of 133 Xenon in water.

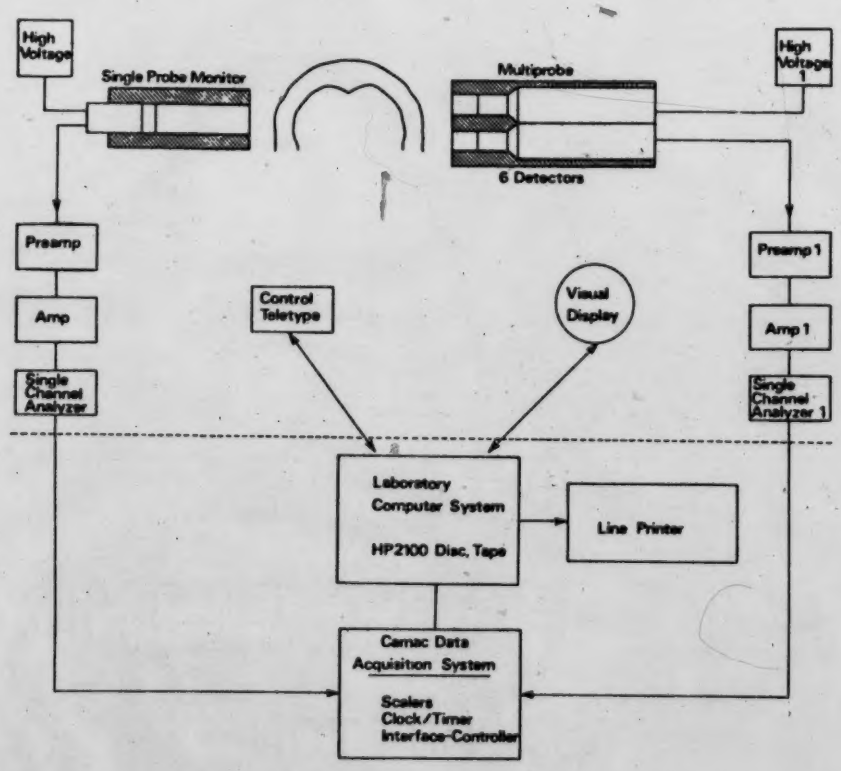

FIG. 12 Schematic diagram of instrumentation for cerebral blood flow studies.

index" (ISI), and biexporential or "compartmental". The "initial-slope index" method was used for all CBF calculations presented in this report. These values may be obtained from the first two minutes of clearance data by calculating the "delay constant" from the approximately exponetial clearance curve. Then:

$$\text{CBF (ISI)} = 100\ g\ \frac{0.693}{T\ 1/2}\ \text{ml/100 gms/min.}$$

g is the partition coefficient (tissue to blood) of the grey matter of the brain.

Comparison of the three methods of CBF calculations in the literature (122) reveal very similar results, although the values of CBF using the ISI method are usually somewhat higher than those for the stochastic or compartmental methods due to a relatively greater contribution from the rapidly cleared regions of the brain (grey matter) to the initial period of data collection. The calculations of CBF presupposes the recorded clearance curve represented a single transit of 133 Xe, i.e. that the tracer does not re-circulate through the counting field. The lungs are a very effective filter for 133 Xe, and for these measurements re-circulation can be disregarded. In the presence of pulmonary insufficiency, however, or when a subject rebreathes his own expired air, significant recirculation may occur and correction must be made in the analysis.

Based upon data obtained in baboons (123), CBF values

corrected for hematocrit and PaCO2 are calculated. However, in this study, the uncorrected values were used because of the uncertainty of the exact response of cerebral blood vessels to PaCO2 after the SAH (89,110). Care was taken during study to keep the PaCO2 between 36 and 44 mmHg.

VI NEUROLOGICAL ASSESSMENT

Neurological assessment of all animals surviving was carried out at 5 hours and again for survivors at 20 hours post-insult. A five division grading system, described by Rothberg (3) was utilized.

GRADE 1 - alert, active, vocal, neurologically sound, accepts food and water, aggressive.

GRADE 11 - lethargic, somnolent, attempts to sit up, sitting or standing but unsteady with poor balance.

GRADE 111 - no spontaneous attempts to become upright, responds to stimulation appropriately (visual, auditory, tactile, painful).

GRADE IV - obtunded, no response to stimulation of any form, remains inactive.

GRADE V - moribund, totally unresponsive, failing vital signs.

Following the neurological assessment at 20 hours the animal was sacrificed and the brain examined grossly to establish the precise site of hemorrhage (Fig. 13). The brains were photographed, weighed, and placed in formaldehyde. Later the brains were sliced to assure than an intracerebral hematoma

FIG 13: Subarachnoid hemorrhage - basal view of brain

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had not been induced.

VII CALCULATION OF CEREBRAL PERFUSION PRESSURE

Cerebral perfusion pressure (CPP) or the pressure of blood perfusing the brain can be calculated as follows:

$$CPP = MaBP - (ICP + ICVP)$$

ICVP being intracranial venous pressure

In this study, central venous pressure (CVP) was measured and is equal to or less than ICVP (124) and is used as an estimate of the ICVP in the study.

therefore, $CPP = MaBP - (ICP + CVP)$

In the comparison of the CPP data with that of Rothberg et al. (6), the CPP was calculated excluding the CVP values.

VIII EXPERIMENTAL DESIGN

The present work is comprised of two separate studies: Study I, a preliminary study of 8 animals used to establish the treatment procedure and protocol; and Study II, a series of 14 animals to assess the effect of the treatment regime on the pathophysiology of SAH.

Study I - Objectives

1. to study the feasibility of employing simultaneous hypertension, volume expansion, and ventilatory assistance as a therapeutic regime post-SAH in a cynomolgus monkey model.
2. to evaluate the pressor response of several vasopressors (norepinephrine, metaraminol, dopamine) post-SAH in the cynomolgus monkey model.

3. to evaluate the method of volume expansion using autologous blood and human serum albumin and assure that any untoward side effects could be avoided or treated if necessary. (i.e. hypocalcemia or pulmonary edema.)
4. to evaluate the angiography and vessel measurement process in order to improve its accuracy, precision, and reproducibility.

Study II - Objectives

1. to investigate the effects of the simultaneous use of hypertension induced with dopamine, volume expansion using autologous blood and human serum albumin, and ventilatory assistance on the pathophysiology of SAH in a cynomolgus monkey model.

IX EXPERIMENTAL PROCEDURE

Following surgical preparation of the animal and placement of the tip of the needle in the chiasmatic cistern, a baseline CBF measurement and angiograms were obtained. On four monkeys in the preliminary study, CBF measurements were made prior to any contrast studies, 10 minutes after the first angiogram, then after placement of the needle tip in the chiasmatic cistern. The SAH (volume 1.67 ml/Kg body weight) was then induced and assisted ventilation instituted immediately because of the apneic spell invariably occurring post-SAH. In the initial animals, the ventilatory assistance was instituted 25 or more minutes post-SAH but this proved to be unsatisfactory and the above noted protocol was quickly established. At 7 to 10 minutes

post-SAH, a CBF study was obtained followed by an angiographic session. The remainder of the treatment regime was then instituted by starting infusions of dopamine, autologous blood and 4 gms/DL albumin. Every half hour up to 3.5 hours post-SAH a CBF study was conducted, and following every second CBF study angiograms were obtained. A minimum of 10 minutes separated any angiographic session and the following CBF study.

At 3.5 hours post-SAH, treatment was continued while the probes and catheters were removed and the wounds resutured. At 5 hours post-SAH the treatment was stopped and the monkey assessed neurologically. Those animals surviving were reassessed neurologically at 20 hours, then sacrificed to verify the site of the hemorrhage. Only the animals with a 90% or greater SAH and no significant intercerebral hemorrhage were accepted into the SAH treatment (SAH-Rx) group.

CHAPTER THREE : RESULTS

Although this work has two study groups; a group of 8 animals in a pilot study, and a group of 14 animals in the main treatment study for a total of 22 monkeys, the results of both groups overlap in certain areas and have been combined in these areas to maintain coherence in the results.

Two experiments were aborted because of technical problems: in one case there was failure to clip the external carotid adequately and repeated attempts resulted in the demise of the monkey; in the other case the animal was sacrificed when fully prepared surgically for the experiment because of an accidental loss of all available 133 Xe. However, this later animal was utilized to obtain good basal views of the cerebral arterial anatomy, and several live peripheral nerves were provided to the physiology department. All results on the remaining 20 monkeys are presented here. All values are given as mean ± standard deviation, unless otherwise indicated.

I PILOT STUDY

The purpose of the pilot study was to establish the precise treatment regime by means of assessing each parameter i.e., the timing of their introduction, the safety of autologous blood in human albumin in transfusion, and the pressor effect of dopamine.

The introduction of assisted ventilation was initially carried out after the post-SAH CBF study and angiographic session, i.e., 30 or more minutes post SAH. This protocol was changed after several animals and ventilation was introduced in the immediately post-SAH period because of the prolonged apneic spell observed in some animals. This experimental situation simulates the condition in the home or on the street where someone is given respiratory assistance by mouth to mouth resuscitation after collapsing and having a respiratory arrest.

Various vasopressors (norepinephrine, metaraminol, dopamine) were used in the post-SAH period in an attempt to increase the blood pressure in these animals. However, none of these agents were effective as vasopressors, except in a few cases, despite high doses of each individual agent. A review of the experimental methodology at this point led to the decision that the d-tubocurarine dose was likely too high resulting in massive histamine release and a "shock like" state (125). Also the hypothesis that the albumin transfusion was resulting in the binding of the ionic calcium, or the anticoagulant used was affecting the ionic calcium was considered. Further support for this second hypothesis was provided by the development of seizures responsive to calcium gluconate in two later monkeys. Also a tachyphylaxis to the alpha properties of dopamine was seen in many animals which responded to the administration of calcium gluconate. In four later monkeys (Table 1) serum

calcium levels were assessed pre-and post-transfusion, prior to the administration of any calcium gluconate, to try and determine the contribution of hycocalcemia to this problem. As seen in Table 1, serum calcium levels in these four animals fell (M-19, M-21, M-22, M-24) but not to what would be considered tetanic levels in the human. None of these monkeys had seizures, and in the two monkeys which did have seizure-like activity, no serum calcium levels were obtained prior to the administration of the calcium gluconate.

After employing a lower dose of d-tubocurarine (0.3 mgm/Kg) with a slightly better pressor response with the dopamine, it was decided to change to another competitive neuromuscular blocker, gallamine.

In the latter part of the preliminary series, it was decided to continue with the dopamine as the single vasopressor to be used because of recent literature documenting its empirical use in SAH (97,98).

Volume expansion using autologous blood in human serum albumin was found to be quite safe on this acute basis in the pilot study, except for the questionable effect on the serum calcium levels. The volume transfused was usually greater than 50% of the monkey's blood volume. Monkey 2 was the only animal that developed overt pulmonary edema with frothy red sputum. The CVP during this episode rose to 16 mm Hg. In no other animal did the CVP climb this high and in later monkeys volume expansion was slowed when the CVP

	MONKEY SAMPLED													
	M-9	M-10	M-11	M-14	M-15	M-16	M-17	M-19	M-20	M-21	M-22	M-23	M-24	MEAN± S.D.
Ca pre-transfusion (mg/DL)	7.5	8.4	8.8.	9.0*	8.0	8.0	7.0	7.1	4.6*	8.3	8.3	8.6	8.9	8.1±0.6 n = 11
Ca post-transfusion (mg/DL)	-	-	-	-	-	-	-	6.0	7.0	7.1	7.5	-	8.0	7.1±0.7 n = 5
Albumin pre-transfusion (G/DL)	2.4	-	2.5	2.6*	2.7	2.8	2.6	2.5	1.5*	2.8	3.0	-	3.1	2.7±0.3 n = 9
Albumin post-transfusion (G/DL)	-	-	-	-	-	-	-	3.6	3.2	3.4	3.2	-	3.9	3.5±0.2 n = 5
Total Protein (G/DL)	6.2	-	6.2	7.1*	7.0	6.9	6.1	6.8	4.3*	7.0	7.1	8.5	7.7	7.0±0.6 n = 10
PO_4 (mg/DL)	4.8	3.7	4.5	8.3*	-	4.9	-	4.0	-	4.3	-	-	5.3	4.5±0.6 n = 7
Na. (m.mol/L)	149	149	146	148*	-	139	132	150	-	-	140	141	149	144±6 n = 9
K. (m.mol/L)	2.9	3.9	4.3	4.5*	-	4.3	3.6	3.8	-	-	3.4	3.9	3.9	3.8±0.6 n = 9
CL. (m.mol/L)	117	114	115	-	-	-	-	-	-	-	-	-	-	115±2 n = 3

* Likely inaccurate and not used in calculating means

TABLE I: Serum values for calcium (Ca) and albumin pre and post transfusion. Serum values for total protein, phosphate (PO_4), sodium (Na.), potassium (K), and chloride (CL) before experiments.

reached 12 mmHg. In most animals this was not a problem, and in fact despite the rapid (1 hour) administration of more than 100 mls of colloid, the CVP often did not rise more than 5 mmHg.

II SUBGROUPS IN PILOT AND MAIN TREATMENT STUDY

Results on all animals have been tabulated and grouped according to the autopsy findings; SAH - pilot study (n = 3, Tables 2, 3 and 4), intracerebral hematoma (ICH) (n = 2, Tables 5 and 6), subdural hemorrhage (SDH) (n = 2, Tables 7 and 8), mixed hemorrhage (n = 4, Tables 9, 10, 11 and 12), SAH-Rx group (n = 9, Table 13). The results on the SAH-Rx groups have been tabulated as a unit in Table 13 because of the similarity of this group with regard to treatment and type of hemorrhage.

A. SAH Group from Pilot Study

The results on the SAH-Rx group from the pilot study, (Tables 2, 3 and 4) are to be viewed with caution due to the use of a toxic dose of d-tubocurarine, the delayed ventilatory assistance (usually 30 or more minutes post-SAH), combined with the lack of expertise of the operator at this time. Hence the rCBF values are low and are reflected in the high morbidity and mortality of this group.

B. Intracerebral Hematoma Group (ICH)

The ICH group (Tables 5 and 6) consists of two animals which are quite different from each other in respects other than the fact that one came from each of the series. Monkey

	FLOW I	FLOW II	FLOW III	SAH + FLOW IV	FLOW V	FLOW VI	FLOW VII	FLOW VIII
		pre-SAH flows		7-10 min	1 Hr.	1.5 Hr.	2.5 Hr.	3 Hr.
mean r CBF (ml/100gm/min)	45	49	35	24	35	62	50	31
MaBP (mmHg)	82	88	73	70	89	133	123	107
ICP (mmHg)	2	12	8	20	26	38	5	10
CVP (mmHg)	4	5	4	5	14	12	15	16
PaCO2 (mmHg)	25	34	29	20	36	34	26	36
PaO2 (mmHg)	120	200	200	180	200	200	310	175
Heart Rate (beats/min)	120	-	-	90	200	200	200	200
Resp. Rate (per min)	28	40	28	30	40	12	-	-
Tidal Volume (ml)	16	19	17	30	50	40	40	40
ICAP (mm)	1.21	-	-	0.82	-	1.18	-	1.08

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for Hem. (sec)	Grade 5 Hrs.	Grade 20 Hrs.	Fresh Brain Wt. (gm)
SAH	3.0	50	150	40	60	4	(Sacrificed at 5 hrs.)	65

TABLE 2: Subarachnoid Hemorrhage, monkey 2

	FLOW I pre-SAH	SAH + FLOW II 7-10 min	FLOW III 1 Hr.	FLOW IV 2 Hr.	FLOW V 3 Hr.	FLOW VI 3.5 Hr.	FLOW VII	FLOW VIII
mean r CBF (ml/100gm/min)	43	41	28	23	34	35	-	-
MaBP (mmHg)	108	104	65	92	100	105	-	-
ICP (mmHg)	4	20	4	30	50	30	-	-
CVP (mmHg)	5	8	9	10	11	12	-	-
PaCO2 (mmHg)	39	47	70	49	49	51	-	-
PaO2 (mmHg)	160	129	175	185	175	148	-	-
Heart Rate (beats/min)	160	160	150	160	160	190	-	-
Resp. Rate (per min)	26	25	13	18	20	20	-	-
Tidal Volume (ml)	50	60	50	50	50	48	-	-
ICAP (mm)	.90	.72	-	.80	-	.71	-	-

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for Hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
SAH	3.15	30	130	20	80	4 (Died 7 hrs. post-SAH)	5	67

TABLE 3: Subarachnoid Hemorrhage, monkey 6

	FLOW I pre-SAH	SAH + FLOW II 7-10 min	FLOW III 1 Hr.	FLOW IV 1.5 Hr.	FLOW V 3.5 Hr.	FLOW VI	FLOW VII	FLOW VIII
mean rCBF (ml/100gm/min)	52	16	14	23	18	-	-	-
MaBP (mmHg)	76	84	84	80	-	-	-	-
ICP (mmHg)	-	-	-	-	-	-	-	-
CVP (mmHg)	6	6	9	6	6	-	-	-
PaCO2 (mmHg)	38	40	55	39	36	-	-	-
PaO2 (mmHg)	135	120	87	152	157	-	-	-
Heart Rate (beats/min)	210	180	180	240	240	-	-	-
Resp. Rate (per min)	26	25	30	30	-	-	-	-
Tidal Volume (ml)	60*	60*	60*	60*	60*	-	-	-
ICAP (mm)	1.04	0.85	-	-	-	-	-	-

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
SAH	2.6	40	140	60	60	5 (Kept alive until 5 hrs. by ventilatory support)	-	58

* Likely inaccurate

TABLE 4: Subarachnoid Hemorrhage, monkey 8

	FLOW I	FLOW II	FLOW III	SAH + FLOW IV	FLOW V	FLOW VI	FLOW VII	FLOW VIII
	pre-SAH flows			7-10 min	1 Hr.	1.5 Hr.		
mean r CBF (ml/100gm/min)	51	51	37	11	18	25	-	-
MaBP (mmHg)	100	100	100	80	75	85	-	-
ICP (mmHg)	3	3	8	95	65	95	-	-
CVP (mmHg)	7	8	8	12	15	14	-	-
PaCO2 (mmHgO	39	34	32	20	55	42	-	-
PaO2 (mmHgO	160	158	160	165	300	325	-	-
Heart Rate (beats/min)	200	150	150	170	200	200	-	-
Resp. Rate (per min)	24	20	25	Intermitt-ent apneic spells.	12	12	-	-
Tidal Volume (ml)	30	30	30	-	30	40	-	-
ICAP (mm)	1.09	-	-	0.66	-	(later angios have no contrast entering brain)		

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for Hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
ICH	3.15	48	148	0	320	5 (Died 2 hrs. post-SAH)	5	70

TABLE 5: Intracerebral Hematoma, monkey 5

	FLOW I pre-SAH	SAH ↓ FLOW II 7-10 min	FLOW III 1 Hr.	FLOW IV 1.5 Hr.	FLOW V 2 Hr.	FLOW VI 2.5 Hr.	FLOW VII 3 Hr.	FLOW VIII 3.5 Hr.
mean r CBF (ml/100gm/min)	41	20	25	31	33	27	31	20
MaBP (mmHg)	97	82	92	104	104	112	115	60
ICP (mmHg)	2	32	36	48	16	28	36	10
CVP (mmHg)	7	8	7	10	8	9	8	6
PaCO2 (mmHg)	36	29	30	38	42	41	35	34
PaO2 (mmHg)	130	137	131	126	144	145	133	118
Heart Rate (beats/min)	240	120	260	220	240	220	170	260
Resp. Rate (per min)	42	28	35	35	38	45	30	25
Tidal Volume (ml)	45	55	35	34	40	40	35	55
ICAP (mm)	0.95	0.75	-	0.83	-	1.03	-	0.91

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for Hem. (sec)	Grade 5 Hrs.	Grade 20 Hrs.	Fresh Brain Wt. (gm)
ICH	3.3	32	132	58	65	5 (Died when removed from respirator)	5	71

TABLE 6: Intracerebral hematoma (ICH), monkey 14

5 probably had a ICH that occurred simultaneously with the SAH induction, resulting in a high ICP. Monkey 14 probably represents a situation in which the ICH accumulated slowly or rapidly during the latter portion of the experiment. The mortality in these animals was high with both animals being dead at 5 hours. Also the wet brain weight was higher than for the other groups (mean wet brain weight 71±1 gm).

C. Subdural Hemorrhage Group (SDH)

The SDH group (Tables 7 and 8) consists of two monkeys with 90% or greater SDH and are both from the second series when the experimental design had been established. The results for these two monkeys for rCBF, MaBP, ICP, vessel calibre (internal carotid above the posterior communicating), and PaCO2 are shown in Fig.14 along with the results from the SAH-Rx group for comparison. Although it is unreasonable to make a statistical comparison between the groups, it is apparent from this figure that the MaBP, ICP and the PaCO2 in the two groups are the same, but the rCBF showed more marked increases in the SDH group with treatment, and the vessel spasm in the SDH group was considerably less than in the SAH group.

D. Mixed Hemorrhage Group

The mixed hemorrhage group (Tables 9, 10, 11 and 12) are those animals with less than 85% SAH yet with no intracerebral hematoma or purely SDH. These particular results are to be viewed cautiously however since a toxic

	FLOW I pre-SAH	SAH + FLOW II 7-10 min	FLOW III 1 Hr.	FLOW VI 1.5 Hr.	FLOW V 2 Hr.	FLOW VI 2.5 Hr.	FLOW VII 3 Hr.	FLOW VIII 3.5 Hr.
mean r CBF (ml/100gm/min)	35	34	57	51	45	59	51	40
MaBP (mmHg)	88	73	98	104	100	96	100	60
ICP (mmHg)	-	-	-	-	-	-	-	-
CVP (mmHg)	8	7	12	7	8	7	12	11
PaCO2 (mmHg)	37	34	41	41	39	44	42	40
PaO2 (mmHg)	130	151	141	144	149	132	142	140
Heart Rate (beats/min)	190	-	210	210	210	210	-	230
Resp. Rate (per min)	35	21	28	28	28	28	28	28
Tidal Volume (ml)	44	50	40	40	60	40	40	60
ICAP (mm)	1.10	1.20	-	0.72	-	0.92	-	0.94

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection time for Hem. (sec)	Grade 5 Hrs.	Grade 20 Hrs.	Fresh Brain Wt. (gm)
S.D.H	2.7	25	125	35	80	2	1	61

TABLE 7: Subdural Hemorrhage, monkey 9

	FLOW I pre-SAH	SAH ↓ FLOW II 7-10 min	FLOW III 1 Hr.	FLOW IV 1.5 Hr.	FLOW V 2 Hr.	FLOW VI 2.5 Hr.	FLOW VII 3 Hr.	FLOW VIII 3.5 Hr.
mean r CBF (ml/100gm/min)	46	27	67	75	76	49	74	71
MaBP (mmHg)	88	76	100	104	101	102	100	96
ICP (mmHg)	4	26	30	30	30	34	30	30
CVP (mmHg)	3	5	6	8	8	9	9	10
PaCO2 (mmHg)	35	35	39	39	43	44	33	38
PaO2 (mmHg)	146	123	138	139	140	139	137	135
Heart Rate (beats/min)	240	220	170	220	200	220	220	240
Resp. Rate (per min)	35	36	34	36	36	26	24	35
Tidal Volume (ml)	50	45	40	45	45	55	55	40
ICAP (mm)	1.06	0.79	-	1.10	-	1.16	-	1.12

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection time for hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
S.D.H.	3.2	32	162	44	41	2	1	60

TABLE 8: Subdural Hemorrhage, monkey 16

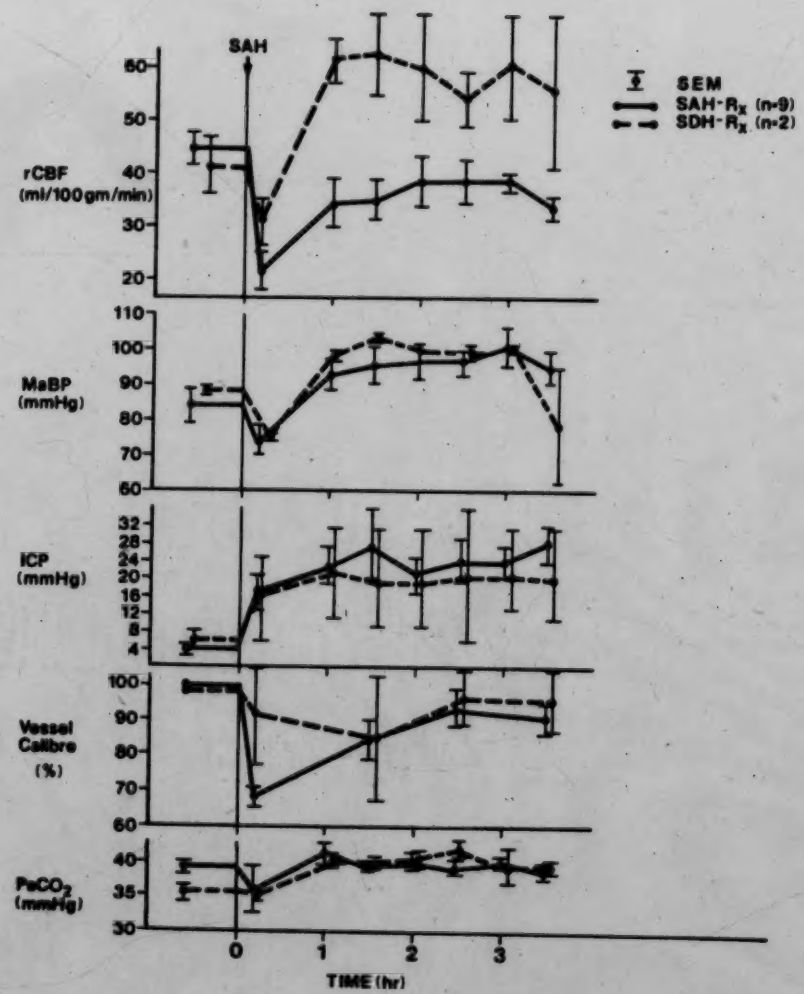


FIG. 14 Regional cerebral blood flow (rCBF), mean arterial blood pressure (MaBP), intracranial pressure (ICP), vessel calibre of internal carotid above the posterior communicating, and partial pressure of carbon dioxide (PaCO2) plotted against time for SAH-Rx and SDH-Rx groups. Note the marked differences in rCBF between the groups despite comparable changes in MaBP, ICP, and PaCO2.

	FLOW I	FLOW II	FLOW III + SAH	FLOW IV	FLOW V	FLOW VI	FLOW VII	FLOW VIII
	pre-SAH flows			7-10 min	1 Hr.	2 Hr.		
mean r CBF (ml/100gm/min)	55	47	41	14	15	22	-	-
MaBP (mmHg)	120	96	87	100	73	73	-	-
ICP (mmHg)	15*	20*	24*	90*	75*	65*	-	-
CVP (mmHg)	6	7	-	-	14	15	-	-
PaCO2 (mmHg)	31	30	32	57	56	37	-	-
PaO2 (mmHg)	135	146	140	42	110	125	-	-
Heart Rate (beats/min)	170	-	-	120	200	200	-	-
Resp. Rate (per min)	45	48	60	30	13	13	-	-
Tidal Volume (ml)	42	42	50	52	34	50	-	-
ICAP (mm)	1.12	-	-	0.95	-	0.66	-	-

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
Mixed	3.15	0	1	120	70	5 (Died 3 hrs. post-SAH)	5	72

*Likely inaccurate

TABLE 9: Mixed Hemorrhage, monkey 3

	FLOW I	FLOW II	FLOW III	SAH + FLOW IV	FLOW V	FLOW VI	FLOW VII	FLOW VIII
		pre-SAH flows		7-10 min				
mean r CBF (ml/100gm/min)	42	41	50	12	-	-	-	-
MaBP (mmHg)	110	100	110	100	-	-	-	-
ICP (mmHg)	35*	36*	18*	75*	-	-	-	-
CVP (mmHg)	11	9	8	11	-	-	-	-
PaCO2 (mmHg)	35	36	37	41	-	-	-	-
PaO2 (mmHg)	120	135	148	70	-	-	-	-
Heart Rate (beats/min)	160	160	160*	160*	-	-	-	-
Resp. Rate (per min)	42	30	24	15	-	-	-	-
Tidal Volume (ml)	25	26	28	40	-	-	-	-
LCAP (mm)	0.98	-	-	0.89	-	-	-	-

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
Mixed	3.6	0	100	90	90	5 (Died 40 minutes post-SAH)	5	55

*Likely inaccurate

TABLE 10: Mixed hemorrhage, monkey 4

	FLOW I pre-SAH	SAH ↓ FLOW II 7-10 min	FLOW III 1 Hr.	FLOW IV 1.5 Hr.	FLOW V 2 Hr.	FLOW VI	FLOW VII	FLOW VIII
mean r CBF (ml/100gm/min)	49	8	13	20	26	-	-	-
MaBP (mmHg)	93	57	90	85	93	-	-	-
ICP (mmHg)	6*	4*	16*	8*	8*	-	-	-
CVP (mmHg)	7	10	9	11	13	-	-	-
PaCO2 (mmHg)	35	36	37	44	44	-	-	-
PaO2 (mmHg)	110	101	90	103	89	-	-	-
Heart Rate (beats/min)	220	140	200	240	260	-	-	-
Resp. Rate (per min)	26	20	20	20	25	-	-	-
Tidal Volume (ml)	65	50	60	60	65	-	-	-
ICAP (mm)	1.18	0.85	-	-	-	-	-	-

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection time for hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
Mixed	3.7	30	130	55	160	5 (Spiked fever and died 2 hrs. post-SAH)	5	60

* Likely inaccurate

TABLE 11: Mixed Hemorrhage, monkey 7

	FLOW I pre-SAH	SAH + FLOW II 7-10 min	FLOW III 1 Hr.	FLOW IV 1.5 Hr.	FLOW V 2 Hr.	FLOW VI 2.5 Hr.	FLOW VII 3 Hr.	FLOW VIII 3.5 Hr.
mean r CBF (ml/100gm/min)	44	19	32	32	32	27	30	31
MaBP (mmHg)	101	54	109	117	108	119	120	107
ICP (mmHg)	4	4	26	36	32	36	28	28
CVP (mmHg)	7	7	10	12	11	11	11	10
PaCO2 (mmHg)	47	45	42	44	48	39	36	41
PaO 2 (mmHg)	136	141	130	117	108	131	141	149
Heart Rate (beats/min)	120	140	156	162	180	186	-	-
Resp. Rate (per min)	30	24	24	25	25	25	24	20
Tidal Volume (ml)	25	40	38	35	45	48	48	45
ICAP (mm)	0.97	0.77	-	0.66	-	0.73	-	0.82

Type of Hemorrhage	Body Wt. (KG)	Blood Transfused (ml)	Total Colloid Transfused (ml)	Apnea (sec)	Injection Time for hem. (sec)	Grade 5 hrs.	Grade 20 hrs.	Fresh Brain Wt. (gm)
Mixed	3.3	34	124	34	68	2	1	57

TABLE 12: Mixed Hemorrhage, monkey 19

level of d-tubocurarine was administered to three animals with varying experimental procedure. However, one monkey (m-19, Table 12) which was treated under the established experimental design, did well, being a neurological grade 1 at 20 hours although the rCBF did not return to normal.

E. SAH-Rx Group

Nine of the 14 monkeys studied after the establishment of the experimental procedure are included in the SAH-Rx group. The results on this group are those which attempt to answer the primary question addressed in this work. The mean values for rCBF, MaBP, CVP, CPP, PaCO2, ICAP, ICBO, MCA, and PPC for each time period can be seen in Table 13 for this group. The results on this group are also shown in graphic form in Figs. 15 and 16, together with results for the "control group".

The body weight of the animals in this group was 3.1±0.4 Kg (range 2.5 to 3.7). The time required for hemorrhage induction was 45±8 seconds (range 32 to 60). All animals had an apneic spell with the hemorrhage induction, the length of which was 41±10 seconds (range 24 to 55) and which was usually terminated by the introduction of assisted ventilation. Length of time between the hemorrhage and the introduction of hypertension and volume expansion was 31±5 minutes (range 26 to 40).

The volume of autologous blood and total colloid transfused into each monkey was 28±6 mls (range 15 to 30),

	FLOW I pre-SAH	SAH + FLOW II 7-10 min	FLOW III 1 Hr.	FLOW IV 1.5 Hr.	FLOW V 2 Hr.	FLOW VI 2.5 Hr.	FLOW VII 3 Hr.	FLOW VIII 3.5 Hr.
mean rCBF (ml/100gm/min)	44±7	22±10	34±11	35±8	38±13	38±7	38±5	34±5
MaBP (mmHg) n = 9	84±15	74±12	93±13	96±14	97±14	97±10	101±14	95±13
CVP (mmHg) n = 9	6±2	7±2	10±2	10±2	10±2	11±3	12±3	10±3
ICP (mmHg) n = 6	4±3	17±9	23±11	27±17	21±10	24±13	24±8	28±11
CPP (mmHg) n = 6	79±15	53±16	63±19	64±24	69±20	64±18	70±21	60±17
PaCO2 (mmHg) n = 9	39±4	36±9	43±5	40±4	41±5	39±2	40±3	38±6
ICBO (%) n = 9	100	70±13	-	84±15	-	89±5	-	94±9
ICAP (%) n = 9	100	68±9	-	84±15	-	93±14	-	91±11
MCA (%) n = 9	100	65±6	-	81±9	-	88±13	-	84±9
PPC (%) n = 9	100	78±16	-	88±21	-	86±10	-	89±10

TABLE 13: RESULTS for r CBF, MaBP, CVP, ICP, CPP, PaCO2, and vessel calibres in SAH-Rx group (mean±standard deviation)

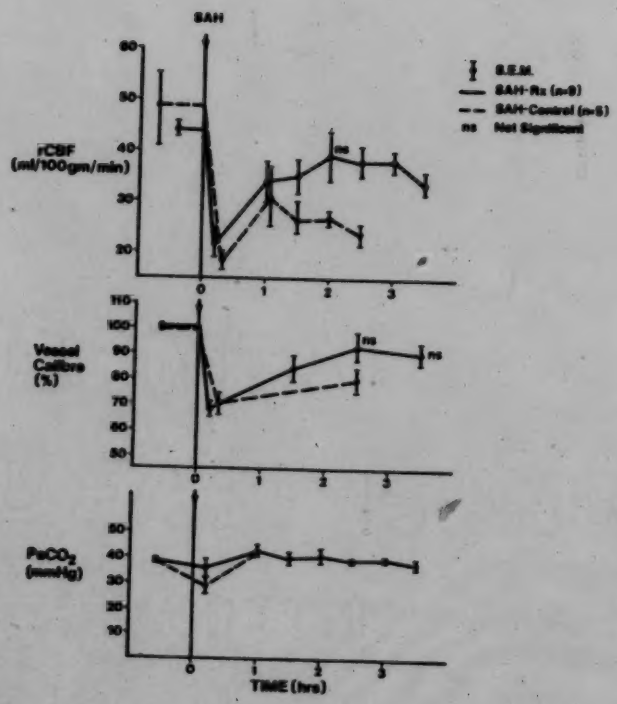


FIG. 15 Regional cerebral blood flow (rCBF), vessel calibre of internal carotid above the posterior communicating, partial pressure of carbon dioxide (PaCO2) plotted against time for SAH-Rx and control groups. Statistical comparisons were made between pre-SAH and post-SAH values for Rx group only.

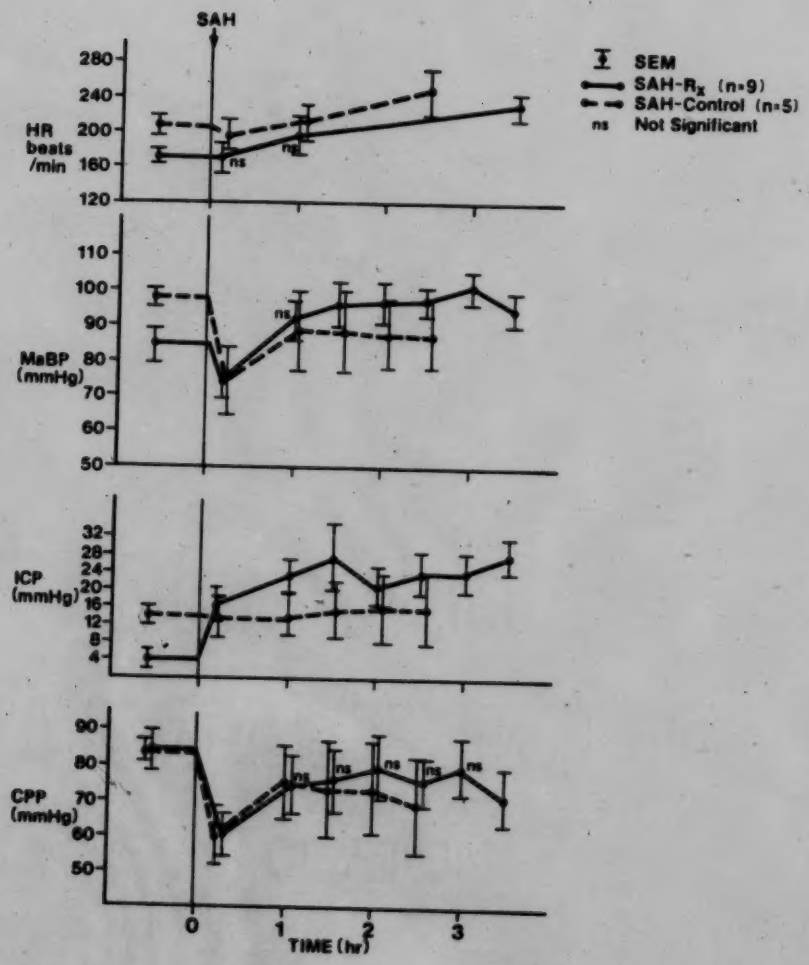


FIG. 16 Heart rate (HR), mean arterial blood pressure (MaBP), intracranial pressure (ICP), and cerebral perfusion pressure (CPP) plotted against time for SAH-Rx and control groups. Statistical comparisons were made between pre-SAH and post-SAH periods for Rx group only.

and 136±15 ml (range 115 to 158) respectively. The CVP rose from 6±2 mmHg pre-SAH to a maximum of 12±3 mmHg at 3 hours post-SAH. The MaBP fell from 84±15 mmHg pre-SAH to 74±12 mmHg immediately post-SAH, and then was elevated by dopamine to a maximum of 101±14 mmHg at 3 hours post-SAH. This represents an increase in MaBP of 20% from the pre-SAH MaBP and 36% from the post-SAH MaBP. The ICP was 4±3 mmHg pre-SAH, 17±9 mmHg immediately post-SAH, then gradually increased to a maximum of 28±11 mmHg at 3.5 hours post-SAH. The CPP fell from 79±15 mmHg to 53±16 mmHg immediately post-SAH, gradually increased to 70±20 mmHg at 3 hours post-SAH and then decreased to 60±17 mmHg at 3.5 hours post-SAH. The heart rate (HR) in the animals gradually increased throughout the study and went from 172±17 beats per minute to a maximum of 233±24 beats per minute at 3.5 hours post-SAH. The HR, MaBP, ICP and CPP from this group can be seen in Figure 16 along with the corresponding values for the "control group" of Rothberg et al. The only appreciable difference is the much higher ICP values in the SAH-Rx group. The CPP values in this figure alone have been calculated omitting the CVP in the equation in order to compare the results with the "control" group.

The rCBF in the pre-SAH period was 44±2 ml/100gms/min. (mean ±SEM), 22±3 ml/100gms/min (mean±SEM) immediately post-SAH, and 38±4 ml/100gms/min (mean±SEM) at 2 hours post-SAH. This value at 2 hours is not significantly different ($P>0.05$) from the pre-SAH flow. The rCBF remained at 38±2

ml/100gms/min (mean ±SEM) at 2.5 and 3.5 hours which is statistically lower ($P<0.05$) than the pre-SAH flow, then fell to 34±2 ml/100gms/min (mean ±SEM) at 3.5 hours post-SAH. These rCBF measurements are presented with comparable data obtained from the "control group" of Rothberg et al in Fig. 15. The rCBF values in the present study are appreciably improved over the "control group" after the 2 hour period post-SAH, although statistical analysis of the results between the two groups has not been done in view of the small number of animals ($n = 3$) in the "control" group during the time periods beginning 1 hour post-SAH.

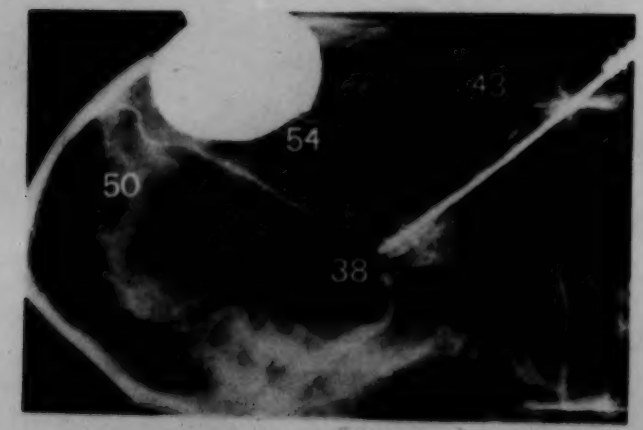
In order to maintain a PaO_2 greater than 100 mmHg and a $PaCO_2$ in the region of 40 mmHg, the tidal volume was increased from 32±7 mls pre-SAH to 46±9 mls immediately post-SAH, and from 49±10 mls at 1 hour post-SAH to 51±6 mls at 3.5 hours post-SAH. The respiratory rate did not change significantly from the pre-SAH value of 29±5 breaths per minute. Pre-SAH, the PaO_2 was 153±4 mmHg and immediately post-SAH, 143±26 mmHg, subsequently falling to 137±31 mmHg at 3.5 hours. Often the N_2O/O_2 ratio has to be decreased to maintain the $PaO_2 > 100$ mmHg. Pre-SAH the $PaCO_2$ was 39±4 mmHg and immediately post-SAH fell to 36±9 mmHg. The maximum value of $PaCO_2$ during the post-SAH period of 43±5 mmHg was seen at 1 hour post-SAH. The mean values for $PaCO_2$ are presented in Fig. 15. The mean $PaCO_2$ value for the "control" group was different only in the immediate post-SAH period. The hematocrit fell from a maximum of 0.35±0.03 pre-SAH to a

minimum of 0.31±0.05 at 3.5 hours.

The decrease in vessel calibre seen with the SAH was most marked in the immediate post-SAH period. The angiographic session held at this time was usually 25 to 30 minutes post-SAH. The spasm was greatest in the MCA, mean vessel calibre being 65±6% and least in the PPC, mean vessel calibre being 78±16% of the pre-SAH values. The mean vessel calibre immediately post-SAH in the ICAP and ICBO was 70±13% and 68±9% respectively. All vessels tended to return towards pre-SAH size during the first 2 hours post-SAH, and at 2.5 and 3.5 hours post-SAH the vessel calibre was not statistically different ($P>0.05$) from the pre-SAH calibre (Table 13). In view of the fact that all four vessel sites measured reacted similarly, only the results from the internal carotid above the posterior communicating are presented in the comparison with the "control group" in Fig. 15. It can be seen that at 2.5 hours the vessels in the "control group" are 20% decreased in calibre whereas the vessels in the SAH-Rx group return to normal.

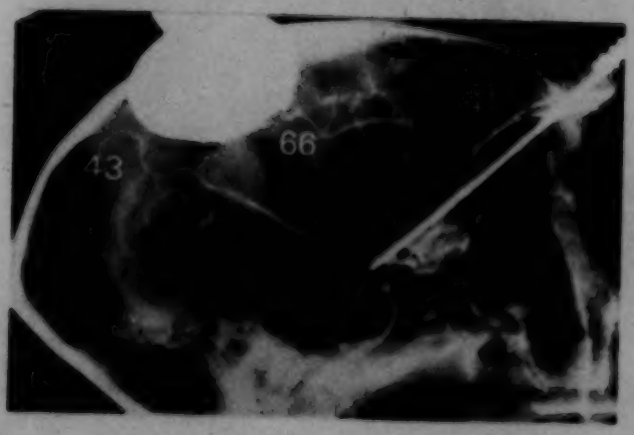
An example of the changes in vessel calibre and rCBF with hemorrhage induction and the response to treatment are shown in Figs. 17 and 18. Diffuse vasospasm can be seen immediately post-SAH with the return of the vessels to normal at 2.5 hours with treatment.

Pearson correlation coefficients were calculated for CBF vs. vessel calibre for each individual vessel, ignoring



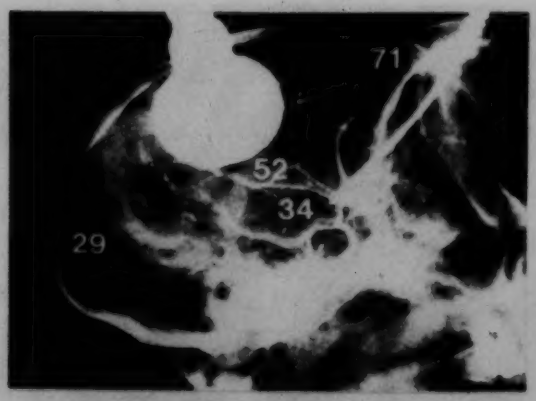
a) $\bar{X}$ Flow 46
PaC02 46
MaBP 96

b) $\bar{X}$ Flow 19
PaC02 40
MaBP 76

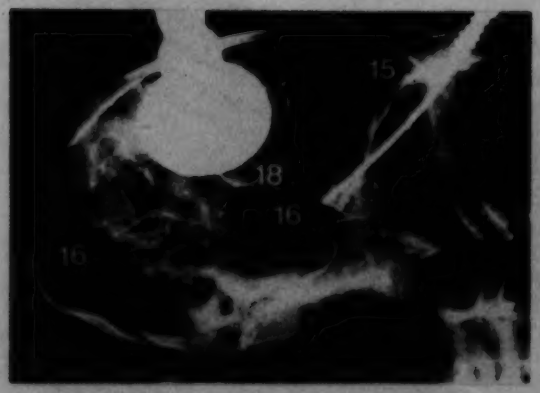


c) $\bar{X}$ Flow 47
PaC02 41
MaBP 103

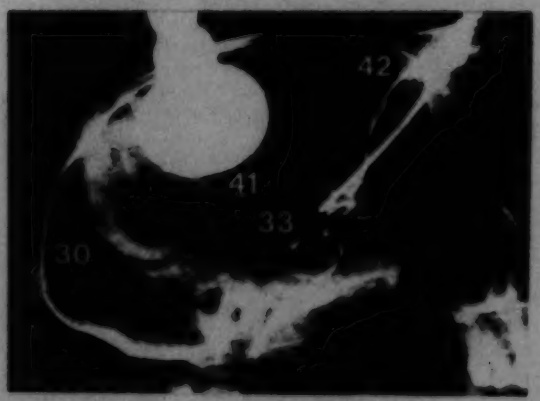
FIG. 17. Example of changes in vessel calibre and regional cerebral blood flow a) pre-SAH, b) immediately post-SAH and c) after 2 hours of treatment. Mean cerebral blood flow ($\bar{X}$ flow), partial pressure of carbon dioxide (PaC02) and mean arterial blood pressure (MaBP) indicated.



a) $\bar{X}$ Flow 46
PaCO2 41
MaBP 62



b) $\bar{X}$ Flow 16
PaCO2 37
MaBP 63



c) $\bar{X}$ Flow 36
PaCO2 44
MaBP 96

FIG. 18. Examples of changes in vessel calibre and regional cerebral blood flow a) pre-SAH, b) immediately post-SAH, and c) after 2 hours of treatment. Mean cerebral blood flow ($\bar{X}$ flow), partial pressure of carbon dioxide (PaCO2) and mean arterial blood pressure (MaBP) indicated

the pre-SAH value, and using the other values as raw data or as a percentage of the pre-SAH value (Table 14). A significant positive correlation is found between CBF and the vessel calibre for ICBO, ICAP, and MCA, but not for PPC. Little difference in the results was found whether or not the raw data, or the data as a percentage of the control value was used.

An analysis of the linear correlation between CBF and vessel calibre was made using the raw data and the data as a percentage of the pre-SAH value. This analysis was carried out twice, controlling and not controlling for changes in CPP. The R^2 value for each vessel (analyzed as a percentage of the pre-SAH value), both controlled and not controlled for CPP is shown in Table 15. In all vessels the correlation with CBF improves when changes in CPP are taken into account. The best linear correlations are found for the ICBO and MCA with R^2 values of 0.35 and 0.34 respectively. These R^2 values indicate that 35% and 34% of the variance in CBF respectively can be explained by changes in angiographic vessel size when changes in CPP are controlled in the analysis. A plot of the linear regression lines for the ICBO, ICAP, MCA, and PPC can be seen in Fig. 19,20,21,22.

The linear regression analysis for CBF in relation to CPP revealed a poor fit ($R^2 = 0.01$), and the Pearson correlation coefficients were not significant ($p = 0.14$ and $p = 0.24$).

Vessel	PEARSON CORRELATION COEFFICIENTS	
	Raw Data	Data as Percent of pre-SAH Value
ICBO[1]	0.65, p = 0.002*	0.58, p = 0.006*
ICAP[2]	0.61, p = 0.003*	0.41, p = 0.040*
MCA[3]	0.61, p = 0.004*	0.60, p = 0.005*
PPC[4]	0.14, p = 0.283[ns]	0.12, p = 0.315[ns]

1. Internal Carotid below Opthalmic
2. Internal Carotid above Posterior Communicating
3. Middle Cerebral
4. Proximal Pericallosal

* Significant
ns Not Significant

TABLE 14: Correlation Coefficients for Individual Vessel Calibres with CBF

	UNCORRECTED FOR CPP		CORRECTED FOR CPP	
	R^2	% Variance Explained	R^2	% Variance Explained
ICBO[1]	0.27	27%	0.35	35%
ICAP[2]	0.12	12%	0.14	14%
MCA[3]	0.27	27%	0.34	34%
PPC[4]	0.01	1%	0.07	7%
CPP[5]	0.01	1%	-	-

1. Internal Carotid below Opthalmic
2. Internal Carotid above Posterior Communicating
3. Middle Cerebral Artery
4. Proximal Pericallosal
5. Cerebral Perfusion Pressure

TABLE 15: Regression Analysis of CBF with Vessel Calibre and CPP both Correcting and not Correcting for changes in CPP

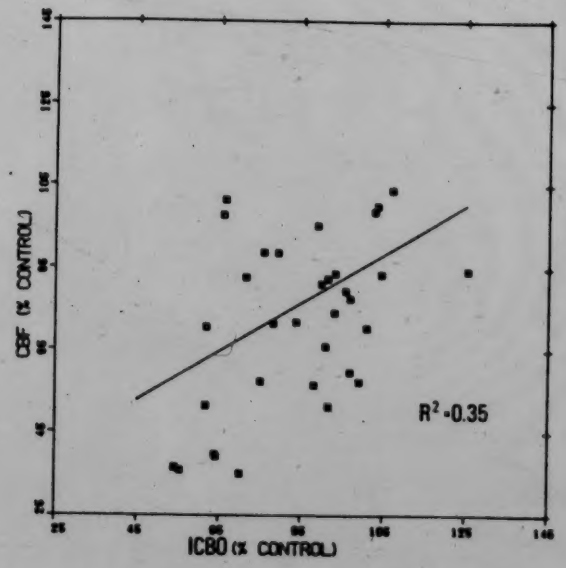


FIG. 19 Linear regression line showing the relationship of CBF with vessel calibre of the internal carotid below the opthalmic artery (vessel calibre and CBF values used were a percentage of the control values)

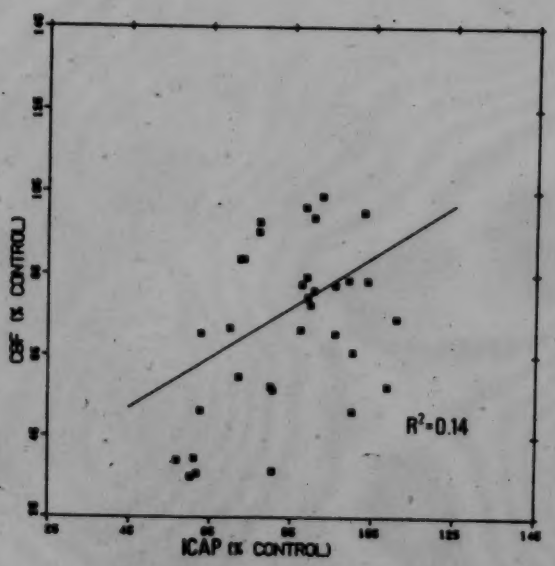


FIG. 20 Linear regression line showing the relationship of vessel calibre of the internal carotid above the posterior communicating (vessel calibre and CBF values used were a percentage of the control values)

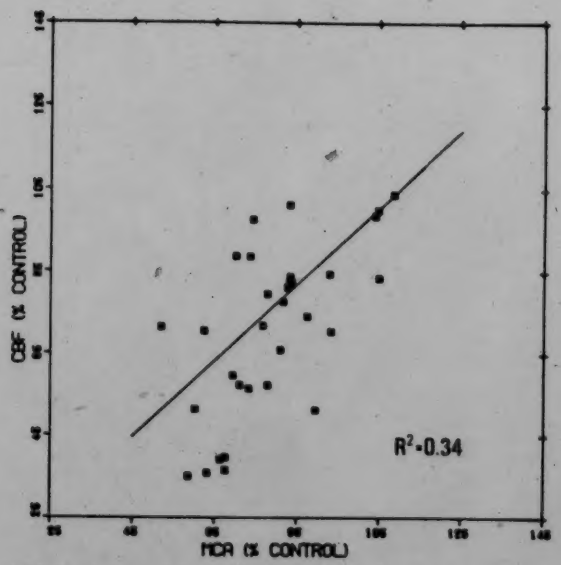


FIG. 21 Linear regression line showing the relationship of CBF with vessel calibre of the middle cerebral artery (vessel calibre and CBF values used were a percentage of the control values).

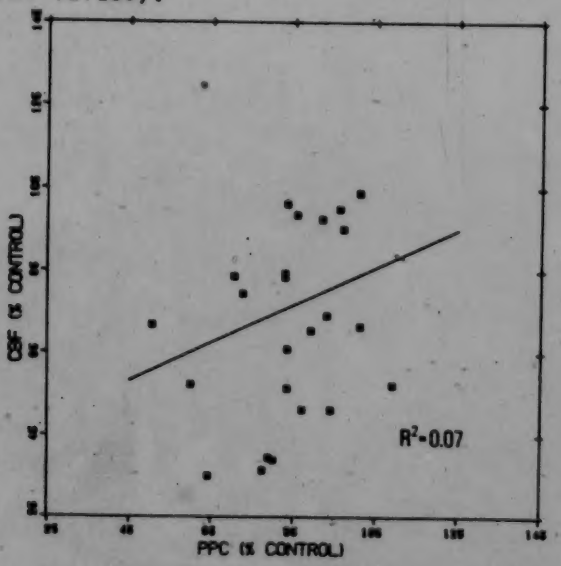


FIG. 22 Linear regression line showing the relationship of CBF with the vessel calibre of the pericallosal artery (vessel calibre and CBF values used were a percentage of the control values).

The mean grade of monkeys in the SAH-Rx group and the "control group" of Rothberg et al can be seen in Table 16. The grade is significantly better for the SAH-Rx group than for the control group at 5 hours ($P<0.05$) and 20 hours ($P<0.01$) post-SAH. This finding confirms the better health status of the SAH-Rx group at both these time periods. A test of proportion was made between the number of animals alive in the SAH-Rx and control group at the 5 hour and 20 hour time periods. At 5 hours a comparison of the proportion of animals alive in the SAH-Rx and "control group" (8/9 vs 3/5) reveals no significant difference, but at 20 hours (7/9 vs 0/5) a significant difference ($P<0.01$) is found.

The wet brain weight for this group is 60±4 gms. (range 54 to 68).

F. Subgroup Results Relating to Hemorrhage Induction

In Table 17 some of the changes in ICP, blood pressure, respiration, and heart rate during the period of SAH induction have been documented according to the final autopsy findings. The SDH and ICH group are too small to make any definite statements but the findings in each group are different in certain areas and these should be noted. The results for the SAH group and the mixed hemorrhage group are comparable except for the increase in half-time decay (time required for ICP to fall to a level one half the difference between peak value and initial resting value) in the mixed hemorrhage group. The SDH group also has a

	Mean Grade 5Hrs	Mean Grade 20Hrs	Alive 5Hrs	Dead 5Hrs	Alive 20Hrs	Dead 20Hrs
SAH-Rx n=9	2.6	2.2	8	1	7	2
Control Group n=5	4.0	5.0	3	2	0	5

TABLE 16: Morbidity and mortality of SAH-Rx and control group at 5 and 20 hours post-SAH.

	TIME TO CHANGE (sec.)			TIME TO PEAK (sec.)		PEAK (mmHg)		HALF-TIME DECAY (sec.)	HEART RATE AT PEAK MaBP (beats/min)
	I.C.P.	MaBP	Resp.	I.C.P.	MaBP	I.C.P.	Systolic B.P.	I.C.P.	
S.A.H. n = 12	9±3	28±2	38±5	51±7	71±7	193±10	206±5	15±6	143±16
S.D.H. n = 2	13±3	28±3	26±4	50±25	60±25	195±5	218±2	28±13	172±88
Mixed Hemorrhage n = 4	6±2	33±3	56±22	78±24	79±25	210±11	223±9	97±51	188±25
Intracerebral Hematoma n = 2	11±1	75±55	75±45	180±120	195±125	220±20	220±10	261±239	66±6

TABLE 17: Changes in ICP, blood pressure, respiration, and heart rate during hemorrhage induction in four major sub-groups. (mean±S.E.M.)

moderately increased half-time decay for ICP. However, the half-time decay for the ICH group is markedly increased due to the contribution of one monkey (M-5) in which the hematoma likely occurred immediately with hemorrhage induction. It should also be noted that the peak ICP in the SAH group (193±10), mean±SEM) is considerably higher than that found in the "control" group for this investigation. (142±17, mean ±SEM) (3). The heart rates for each animal at the peak MaBP was highly variable, ranging from a bradycardia of 60 beats per minute to a tachycardia of 240 beats per minute, and hence a large standard error is often seen.

An example of the changes in ICP, blood pressure, ventilation, and CVP for an induced SAH can be seen in Fig. 23. In this figure, it can be seen that the blood pressure fell initially before increasing, typical of a SAH (126). The apneic spell was 40 seconds and was only terminated by the use of a respirator. Also of note, there is rapid fall in the ICP back to low levels after cessation of the injection of blood while the blood pressure very slowly drops down to pre-SAH levels.

III ANGIOGRAPHY

Findings relating to the changes due to contrast medium, and the accuracy and precision of the vessel calibre measurements are documented briefly in this section.

In the first four monkeys studied, rCBF measurements

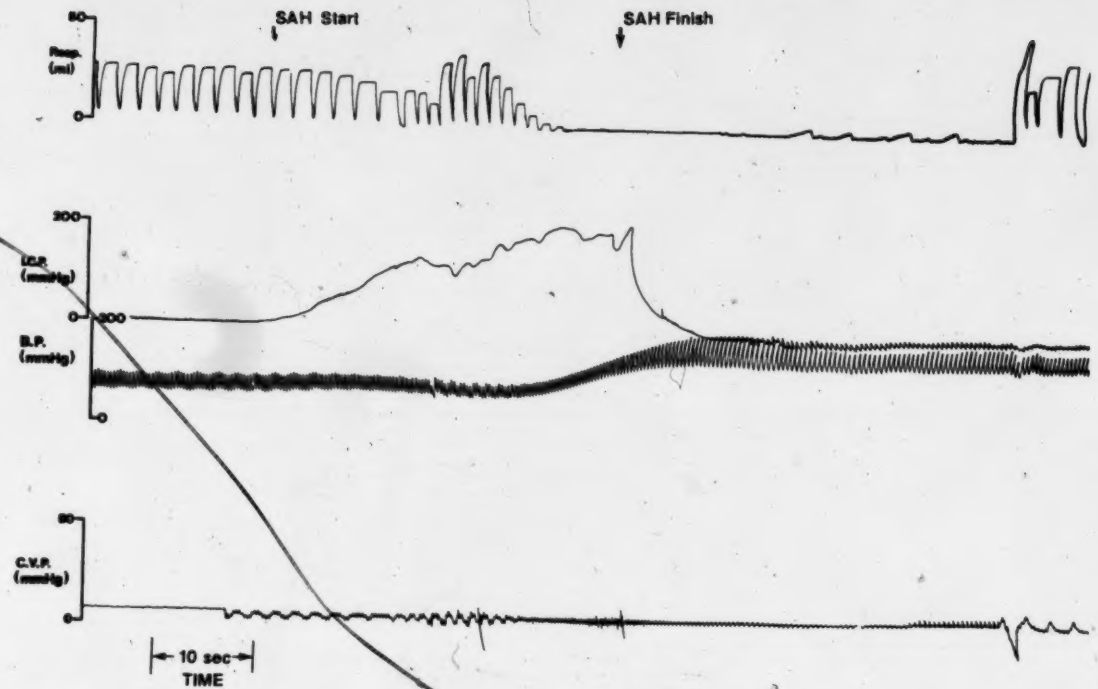


FIG. 23 Sample tracing of changes in respiration (Resp.), intracranial pressure (ICP), blood pressure (BP), and central venous pressure (CVP) during the period of SAH induction. Note the prolonged apneic spell which was terminated by use of the respirator, the rapid fall of ICP down to low levels, and slow fall of BP after the hemorrhage was given.

were made before the injection of any contrast medium, 10 minutes after the injection of contrast medium, and after the placement of the tip of the needle in the chiasmatic cistern. The mean rCBF values at this time were 48±6, 47±4, and 41±7 ml/100gms/min respectively. Although this group comprises only 4 monkeys, tests of comparison within the group reveals no statistical difference in the flow values.

Statistical comparison of 20 measurements from the radiopaque plate placed on the cassette to control for changes in film, screen, exposure and developing characteristics revealed no statistical differences between the angiograms during each separate experiment. However, in one study the measurements of the standard revealed that some factor has changed with the result that the holes were 14% larger than average throughout that particular experiment. The average coefficient of variation for the control plate measurements established from 50 plates was 4.0±0.7%.

Comparisons were also made between the vessel calibres in the first and second films obtained at the angiographic sessions, for 40 vessel pairs with automatic injection and 67 vessel pairs with hand injection. No statistical difference was found between the vessel calibres in the first or second films obtained at an angiographic session using either method of injection. However, the automatic injection of contrast medium resulted in a less marked

variation in the measured vessel calibres and in vessels that were easier to measure by optical techniques. The average coefficient of variation for this system of measurement established on the first 96 vessels measured was 5.3±2.1%.

IV INCIDENTAL HEMATOLOGICAL AND BIOCHEMICAL FINDINGS

All monkeys were bled two to four weeks prior to the procedure by means of a 16 gauge catheter placed in a vein on the dorsum of the leg. In the initial monkeys, blood sampling for hematocrit alone was done at this time, and in later monkeys sampling for hematocrit and biochemical analysis was made.

The mean volume of blood removed from the 22 monkeys was 31±9 mls. The mean hematocrit values at the time of bleeding, and at the experiment 3 to 4 weeks later, was 0.33±0.01 (mean±SEM) and 0.38±0.01 (mean±SEM) respectively. A significant improvement in hematocrit is seen following the administration of parenteral iron despite the removal of a relatively large volume of blood (15% of the blood volume).

In 14 monkeys, one milliliter of blood was allowed to clot and subsequently centrifuged to obtain the serum. The serum was later analyzed for calcium, albumin, total protein and when possible, for sodium, potassium, chloride, and phosphate. In 5 monkeys, a serum sample was also obtained following transfusion of most of the blood and the albumin,

and was used for a repeat analysis of the calcium and the albumin. These values can be seen in Table 1. As mentioned previously, a fall of 1mg/D.L. is seen in the mean serum calcium post-transfusion.

CHAPTER FOUR : DISCUSSION

The purpose of this work was to study the pathophysiologic response to a treatment regime comprising hypertension induced with dopamine, volume expansion, and ventilatory support, in an experimental model of SAH. The efficacy of this regime was to be assessed on the basis of changes in regional CBF, vessel calibre, and particularly, morbidity and mortality in comparison to a comparable series of 5 animals which received a subarachnoid hemorrhage but no treatment. An initial pilot study of 8 animals was conducted to decide on the precise treatment protocol, followed by the main treatment study of 14 animals.

The treatment of the initial 8 monkeys studied is confused by several factors, including the time ventilation was introduced, the toxic dose of d-tubocurarine given to each animal, and a lack of expertise and familiarity of the operator with the experimental model. Hence no conclusions from this group with respect of CBF, vasospasm, and morbidity can be made. However, the results from the pilot study greatly aided in the experimental design of the subsequent studies.

Ventilation of the animals in the post-SAH period was an integral part of the design of this experiment. It has been demonstrated by previous work in this laboratory that ventilatory disturbances are universal immediately following the hemorrhage. Comparison between results from experiments

in which the monkey was ventilated (4,5) and which the monkey was breathing spontaneously (3) suggests that these disturbances play a role in the demise of the animal. This suggestion was borne out in the pilot study when the need to introduce ventilation immediately in order to reduce the apneic spell to less than a minute post-SAH, was found to be necessary. In many of the animals in which ventilation was not supported immediately post-SAH, the CBF never recovered. This may have been due to the other factors involved at that time such as the lack of expertise of the operator and the d-tubocurarine but none the less when immediate ventilatory support was introduced a marked improvement in the animals became apparent.

The pilot study also verified that it was safe to bleed these animals then expand the intravascular compartment with the autologous blood and human serum albumin amounting to volumes up to 50% of each animals blood volume.

The pilot study also served to confirm the use of dopamine as a mild vasopressor in this species of monkey. Further, it served to initiate methods to improve the quality of angiography.

The use of calcium gluconate to control the seizure-like activity of the animals in the later portion of the study, was never verified by documentation of a hypocalcemic state in a seizuring animal. Although the binding of the calcium by the transfused albumin was considered a possible

cause for the seizures, no documentation of this possibility could be found in the literature. However, the possibility that the available calcium was decreased but not to tetanic levels by the albumin is supported by the tachyphylaxis to dopamine. The other possible cause of hypocalcemia is the known effect of ACD anticoagulant on serum calcium levels in humans (127). The seizure-like activity was only seen in the later animals when the ACD was used but it was transfused in such small amounts that hypocalcemia is an unlikely complication of its use. The other possibility that the myoclonic jerks were simply a direct result of the subarachnoid blood and the cessation of the seizures in the two animals in which they occurred with the calcium gluconate, was completely coincidental.

An interesting finding in this study, is the increase in the animals hematocrit between the time of bleeding and the experiment. This suggests that many of the animals are iron deficient when they arrive at the vivarium, and perhaps in future studies, all animals should be given intramuscular iron upon arrival.

The uniformly, rapidly fatal consequences of an intracerebral hemorrhage as indicated by this complication in 2 animals is comparable to the poor prognosis of this event in clinical practice. In this group of animals, the ICP remained high for a relatively long time after the hemorrhage induction and this was probably the major factor

in the demise of these animals.

The SDH-Rx group, although small, is interesting because of the marked differences between this group and the SAH-Rx group. The SDH-Rx group demonstated minimal vessel spasm immediately post-hemorrhage (diameter of ICAP at 7 to 10 minutes 92% pre-hemorrhage diameter), which increased slightly at 1 hour. The rCBF values in this group fell initially but then increased to hyperemic levels (CBF 150% of pre-hemorrhage CBF), with treatment. This hyperemia contrasts markedly with the changes in CBF seen in animals in the SAH-Rx group. These differences in CBF occurred despite no apparent differences in mean arterial blood pressure, intracranial pressure, or PaCO2 between the SDH-Rx and SAH-Rx groups. This demonstrates an ability of this treatment regime to increase CBF above normal levels in animals with no SAH, but with a space occupying lesion, SDH. It is possible that this increase in CBF would have been seen without treatment and represents post-ischemic hyperemia (128). (The ischemic insult resulting from the period of hemorrhage induction when ICP is very high). That it represents post-ischemic hyperemia is unlikely as it has never been seen in previous experiments in this laboratory. More likely there has been some impairment of autoregulation with the ischemic episode and the treatment regime has been able to increase CBF markedly because of the absence of significant vasospasm.

Three of the four animals with a mixed hemorrhage are from the initial 8 animal group, thus leaving only one animal to be compared with the other animals in the series. Any conclusions or deductions from this single animal are impossible and hence there will be no further discussion of this group.

Comparison of the SAH "control group" (n = 5) of Rothberg et al (6) and the SAH-Rx group (n = 9) reveals substantial differences.

The CBF values pre-SAH, immediately post-SAH, and at one hour post-SAH were similar, but after this time, the SAH-Rx group had appreciably higher CBF than the control group. In view of the fact that only values from 3 animals are contributing to the later values in the SAH "control group", it was felt that statistical analysis between the groups might be misleading. However, the later flows of the SAH-Rx are statistically higher than for the SAH "control group" ($P<0.01$).

The higher CBF values are associated in the SAH-Rx group with the return of vessel calibre to the pre-SAH values at 2.5 and 3.5 hours, whereas vessel calibres remain at 80% of the pre-SAH value in the SAH "control group". These changes are associated with a marked improvement in morbidity and mortality of the SAH-Rx treatment group as a whole.

The SAH-Rx group (n = 9) served as the subgroup of animals to assess the efficacy of the treatment regime.

The effect of the treatment of these animals with hypertension, volume expansion, and ventilatory support was marked improvement in the survival and morbidity of the group, associated with moderate increases in CBF and vessel calibre. The contribution of each modality in the regime to the overall benefit cannot be distinguished. Further, each modality may have acted synergistically with the other parameters.

The ventilatory support of these animals in the immediately post-SAH period cannot be underestimated. Soon after the introduction of ventilation post-SAH the animals would usually fight the ventilator, suggesting that the initial resuscitative measures are needed to maintain a good PaO2 only in the period immediately post-SAH. Beyond that stage, ventilatory support is not crucial. In other words, it may be that the apneic spell in association with the raised intracranial pressure and falling blood pressure post-SAH, may result in irreversible changes in the brain which can be prevented by early support of the ventilation in this model.

If disturbances in ventilation have a vital role in the survival of this model, then the need for a SAH "control group" in which only ventilation was introduced would aid the assessment of the contribution the other modalities in

this treatment regime. The absence of this group in this study is due to the paucity of time in which the investigator has to work in this area, combined with the expense and scarcity of non-human primates available for research purposes. The lack of this control group rests as a major flaw in this study and should be kept in mind in the assessment of the results as a whole.

In the SAH-Rx group, the mean arterial blood pressure was increased to a level 20% above the pre-SAH value and CPP returned to the pre-SAH range despite substantial increases in ICP with treatment, as compared to the control group in which the ICP was relatively constant. Nevertheless, in the SAH-Rx group, CPP is not different from the SAH "control group" values. This finding suggests that if dopamine is an active agent in the treatment regime its effect is unlikely to be the result of its vasopressor properties. As indicated in the introduction, there is a moderate amount of evidence suggesting a local effect of dopamine on vascular smooth muscle. It has been shown to activate adenyl cyclase in the brain and kidney and thus increases cAMP concentrations in these areas (115,116). The receptors for dopamine on vascular smooth muscle have also been shown to be different than for beta-adrenergic and cholinergic agents, which allow it to be effective when other drugs are blocked or are in effective (112,113,114). However, the precise action of dopamine on cAMP concentrations in cerebral vascular smooth muscle is unresolved and more research in this area is

needed.

Another possible effect of dopamine on CBF relates to it's inotropic properties. When dopamine is infused in man resulting in increased blood flow to the kidney, the same proportion of cardiac output goes to the kidney (129). Thus if the same proportion of cardiac output is going to the brain, yet the cardiac output is increased due to the inotropic effect of dopamine, then CBF will be proportionally increased. Von Essen (130) has shown that high doses of dopamine in dogs will increase CBF by 30%. This finding suggests that dopamine in this situation supercedes the normal autoregulation of CBF.

The contribution of volume expansion to this treatment regime is likely multifactorial. A recent paper (105) has indicated that the red blood cell mass and total blood volume are decreased in patients post-SAH. Possible causes for these changes in blood volume include bed rest, supine diuresis, pooling in the peripheral vascular beds, negative nitrogen balance, decreased erythropoiesis, and iatrogenic blood loss. Some of these factors are certainly present in the animal model employed in this study. In particular, there is the iatrogenic blood loss, the equivalent of bed rest as these animals have been confined to a small cage for several months, and the negative nitrogen balance and decreased erythropoiesis associated with the confinement and change in the monkeys' diet.

Other effects of volume expansion could be to increase cardiac output, which may occur under certain circumstances when the pre-load on the heart is increased (106,107,108). This increase in cardiac output may in turn increase CPP and CBF.

The use of 4 gm per DL albumin may have acted in a comparable fashion as mannitol, and by maintaining the colloid osmotic pressure within the circulation, it may have aided in maintaining the ICP at lower levels. As already noted, the intracranial pressure was markedly increased with the treatment regime lowering the CPP to levels comparable to the SAH "control group". This underlines the need to monitor ICP in patients in which this regime is used so that if marked increases in ICP are seen with significant falls in CPP, then appropriate measures to reduce the ICP may be taken.

Another factor involved in volume expansion is the maintenance of a good hematocrit with the transfusion of whole blood or packed cells. This increases the oxygen carrying capacity of the blood and permits the transport of more oxygen to ischemic areas.

The results have indicated that a significant positive correlation between the vessel diameter of the ICBO, ICAP, and MCA with CBF is present even though maximum vasospasm in these vessels was in the range of 30 to 35% of their pre-SAH

vessel calibre. The factors which may affect CBF in the aftermath of SAH are multiple. As the PaCO2 has been kept relatively constant and correction in the results for changes in MaBP, ICP, and CVP have been made, then the changes in CBF should then be dependent on either angiographical vasospasm or changes in the microcirculation such as microvascular vasospasm or "sludging" of the blood elements. The regression analysis reveals that at most, 35% of the variance in CBF is dependent on changes in angiographically demonstrable vasospasm. This means that some other factor or factors are having a proportionately greater effect on the changes in CBF.

The logical conclusion is that there have been changes at the microvascular level which are altering the CBF in the post-SAH period. This conclusion would support what previous workers in this laboratory have found (3,4,5); that angiographic vasospasm is not the most significant factor involved in the control of CBF post-SAH. However, the good correlation between CBF and vessel calibre demonstrated with the Pearson correlation coefficients suggests that any changes occurring at the microvascular level, are reflected in the angiographic vasospasm so commonly seen post-SAH. Whether or not the mechanism for the changes at both levels is comparable or if one can occur without the other, is undetermined.

Finally the vasospasm seen in this study was moderate

and in the range of 30 to 35% of the vessel calibre. It is possible that when vasospasm is more severe that it has a proportionately more pronounced effect on the decreases in CBF seen with SAH.

In this study, attempts were made to improve the technique involved in the angiography such that accurate reproducible angiograms could be made. Further it was of concern that the contrast medium used did not alter the CBF measurements.

The effect on CBF of the contrast medium was studied in four of the initial animals; no significant alterations in CBF occurred when these measurements were made more than 10 minutes following the last angiogram. The literature on the effect of contrast medium on CBF indicates contrast medium will temporarily increase CBF in the non-traumatized brain, but can temporarily decrease CBF in the presence of subarachnoid blood (131,132,133,134). This small series supports the accuracy of CBF measurements if carried out more than 10 minutes following the injection of contrast medium. The use of hand injection of contrast as opposed to the use of an automatic injector was studied. The automatic injector resulted in angiograms which were easier to assess under optical magnification. Also there were less marked swings in vessel diameter on the two films obtained at each angiographic session using the automatic injector, but statistical analysis did not demonstrate any significant difference between the first and second film using either method of injection. This suggests that errors involved in the image production and measurement are of such a magnitude that superiority of one system over the other can not be shown. The hand injection of the contrast results in the use

of less contrast medium and also prevents any mishaps resulting in the injection of large volumes of contrast from a malfunctioning automatic injector.

The automatic injector is advantageous because no one needs to be near the animal during the radiographic exposure and hence reduces radiation exposure to the operators. Also, it allows control over the pressure of injection, and the timing of the radiographic exposure in relation to the injection. Therefore, some of the variables which could possibly contribute to changes in vessel calibre are controlled. As already noted, variation in vessel calibre due to changes in these factors with hand injection could not be shown, possibly as a result of limitations in the optical measuring system combined with the unsharpness of the radiographic image.

The use of a brass control plate revealed that during any given experiment, no significant change occurred in film, screen, exposure or developing factors. However, in view of the demonstration of a 14% change in the hole diameters due to an alteration in one of these factors in one experiment, a plate of this nature is important if comparison of the absolute vessel calibres is to be made. This also suggests that clinical studies of vasospasm are limited in their accuracy because control of these factors is not carried out.

The coefficient of variation, 5.3±2.1%, represents the

variability in measurements due to all factors which alter the image quality plus the observer characteristic response (i.e. the overall ability to decide where the edge of the vessel is in order to measure it). No changes in vessel calibre are likely to be significant unless they are twice the size of the coefficient or above 11 to 15%. In other words, changes in vessel size of 2 times the average coefficient of variation (%standard deviation) are significant vessel changes (i.e. unlikely to occur by chance alone because of the variability of measurements).

The angiograms in this study are reproducible using hand or automatic injection of the contrast medium and the selection of any film in good arterial phase results in no bias or significant alteration in the vessel calibres. The control of factors such as changes in film, screen, exposure, and developing are important if accurate reproducible measurements are desired. Finally, the average coefficient of variation established in this study would suggest that changes in vessel calibre of less than 15% are not significant.

In summary our results have demonstrated a dramatic improvement in the morbidity and mortality of monkeys post-SAH when a treatment regime of hypertension induced with dopamine, volume expansion using autologous blood and human serum albumin, and ventilatory support are instituted.

However, there are certain limitations to the extrapolation of this study to the human situation where this regime is used to treat ischemic complications post-SAH. The first of these limitations, as already noted, is the lack of a control group in which ventilation only was introduced. There is a possibility that ventilation is the single, most important parameter which results in the improved morbidity and mortality in this model. This possibility exists despite the apparent benefits of controlled hypertension and volume expansion in ischemic complications post-SAH documented in the literature.

The other major limitation of this model is the "acute" nature of these studies. The use of this particular treatment regime in man is usually initiated several days to a week post-SAH, and most often in the post-operative period. The fact that this treatment regime is beneficial in the acute situation does not guarantee its success in the more delayed ischemic complications post-SAH. The need for the development of a chronic SAH model in this laboratory is acknowledged.

Despite these limitations we are justified in making

the following conclusions from this study.

1. The combined regime of hypertension induced with dopamine, volume expansion, and ventilatcry support are efficacious in the treatment of acute cerebrovascular disturbances post-SAH.
2. The benefit of controlled hypertension post-SAH may not be due to a simple pressor effect as no significant increases in CPP was seen as a result of the moderate increases in ICP post-SAH with treatment. Rather, pressor agents such as dopamine may have a local effect on the cerberal vasculature, as well as it's positive inotropic effects on the heart which may increase CBF.
3. The universal ventilatory disturbances seen immediately following large volume SAH contribute significantly to the morbidity in this model.
4. The microvasculature plays a major role in the CBF disturbances seen post-SAH when the vasospasm of the angiographic vessels is of a moderate degree (30 - 35%).

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